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The Official Journal of the International Union Against Tuberculosis and Lung Disease

**ABSTRACT BOOK**

**51st World Conference  
on Lung Health of the  
International Union Against  
Tuberculosis and Lung Disease (The Union)**

**VIRTUAL EVENT  
20 OCTOBER – 24 OCTOBER 2020**

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Since its foundation in 1939, the mission of the Research Institute of Tuberculosis, Japan Anti-Tuberculosis (RIT/JATA) has been to contribute to domestic and global tuberculosis control by conducting various studies, providing technical support as well as performing activities for international cooperation and collaboration.

## Our Vision

- ▶ A world where no one suffers from tuberculosis

## Our Mission

- ▶ Our mission is to eliminate TB suffering through development and implementation of comprehensive TB control strategies.



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# The International Journal of Tuberculosis and Lung Disease

SUPPLEMENT 2

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## SYMPOSIA:

### WEDNESDAY, 21 OCTOBER 2020

- S1 SP-01 Strengthening evidence on optimal treatments for multidrug-resistant TB: approaches to studying timing and duration.
- S2 SP-02 Tests for the detection of TB infection - tuberculin skin test vs interferon-gamma release assays
- S3 SP-03 When novel product bans are best: lessons learned and challenges faced in tackling tobacco in low-and middle-income countries.
- S4 SP-04 Advancing TB prevention in children during the COVID-19 pandemic
- S5 SP-05 Updating World Health Organization TB screening guidelines: evidence reviews of the yield, tools and costs of screening
- S6 SP-06 The people-centred framework for national and subnational TB planning and programming: early adopters share lessons learned and experiences
- S7 SP-07 Towards new TB vaccines: progress and considerations for introduction
- S8 SP-08 Incarceration for drug use and TB among people who use drugs: time to break the cycle
- S9 SP-09 Ending TB in vulnerable populations through operational research, capacity building and evidence-informed decision making in Eastern Europe and Central Asia (Find-Treat-All).
- S10 SP-10 High-dose rifapentine with or without moxifloxacin for shortening treatment of TB: TB Trials Consortium study 31/ACTG A5349 phase III clinical trial results

- S11 SP-11 Treating mild asthma: a paradigm shift
- S12 SP-12 Scale-up of joint action on diabetes and TB: lessons from the field
- S13 SP-13 Deadly partners - COVID-19, non-communicable diseases and tobacco
- S14 SP-14 Is TB elimination in the European Region a realistic goal?

## SYMPOSIA:

### THURSDAY, 22 NOVEMBER 2020

- S15 SP-15 Short, all-oral regimens for rifampicin-resistant TB: progress towards programmatic implementation at country level.
- S16 SP-16 Health system response preventing TB and tobacco: lessons learned from COVID-19
- S17 SP-17 Detecting TB among people living with HIV: updated options with updated guidance
- S18 SP-18 The work of the WHO European Laboratory Initiative on TB, HIV and viral hepatitis
- S19 SP-19 Household and close contact investigation: a key gateway to TB prevention and case detection in children
- S20 SP-20 Improving access to laboratory-based diagnosis for young children: recent advances using stool and urine as alternative sample types
- S21 SP-21 Engaging communities to address concurrent pandemics of TB and COVID-19
- S22 SP-22 Advancing a prevention research agenda for TB

- S23 SP-23 Preventing TB in people with diabetes mellitus: where are we now and where are we going?
- S24 SP-24 The impact of COVID-19 on TB research and development and access: it's a two-way street
- S25 SP-25 It takes more than bandwidth - using the Extension for Community Healthcare Outcomes virtual community of practice model to build local health workforce capacity.
- S26 SP-26 Leveraging a multiplex platform for TB, HIV and coronavirus for diagnostic testing and clinical monitoring: country experiences

**SYMPOSIA:**

**FRIDAY, 23 NOVEMBER 2020**

- S28 SP-27 Exploring existing and potential uses of artificial intelligence for TB programming
- S29 SP-28 My care, my metrics: why patient definitions of person-centred care are critical
- S29 SP-29 TB in pregnancy: what's new in prevention and treatment?
- S30 SP-30 Towards a TB-free childhood: best practices to find, cure and prevent TB in children in Africa
- S32 SP-31 Challenges and issues in ensuring continuum of care for migrants crossing borders with TB.
- S33 SP-32 Regional studies that are improving the zoonotic TB scientific evidence base
- S33 SP-33 Role and contribution of algorithm and score for diagnosis of paediatric TB
- S35 SP-34 Human rights and tobacco: progress and next steps for protecting populations from tobacco industry interference in child health
- S36 SP-35 Migration journeys and the risk for TB – what do we know and what do we need to find out?
- S37 SP-36 Human-centred design to advance patient-centred TB care in low-income countries

- S38 SP-37 Strategies for addressing barriers for LGBTQIA in accessing high quality TB care: a comparative analysis with HIV
- S38 SP-38 Hidden, but for how much longer? The epidemiological and economic burden of post-TB
- S39 SP-39 National TB prevalence surveys in Southern Africa: key results, lessons learned and programmatic implications
- S40 SP-40 Implementation and scale-up of TB preventive treatment: overcoming challenges to reach people living with HIV

**SYMPOSIA:**

**SATURDAY, 24 NOVEMBER 2020**

- S42 SP-41 Preventing human rights abuses in the digitisation of the TB and COVID-19 responses
- S43 SP-42 Take home messages for active case finding learned from TB prevalence surveys, TB or not TB?
- S43 SP-43 COVID-19 in pregnant women
- S44 SP-44 Self-clearance of Mycobacterium tuberculosis infection: needs and consequences
- S45 SP-45 Modelling to advance prevention
- S46 SP-46 Subclinical TB disease: lessons and questions from field to lab
- S47 SP-47 Youth mobilisation to boost the fight to End TB
- S48 SP-48 Understanding the impact of participatory approaches in developing sustainable TB policies



**ABSTRACT PRESENTATIONS  
WEDNESDAY, 21 OCTOBER 2020**

**ORAL ABSTRACT SESSIONS**

- S49 OA-01 TB preventive therapy in HIV
- S53 OA-02 Finding a needle in the haystack: where are children with TB?
- S57 OA-03 Optimising lung health beyond TB
- S61 OA-04 A holistic approach: experiences from Europe
- S65 OA-05 Innovative TB diagnostics
- S69 OA-06 Different approaches to improve treatment and care
- S72 OA-07 Moving away from isoniazid for TB preventive treatment
- S76 OA-09 What person-centred care really means

**E-POSTER SESSIONS**

- S80 EP01 Resisting the resistance
- S86 EP02 Challenges for randomised controlled trials on TB treatment
- S90 EP03 Digital technology in the fight against TB
- S96 EP04 Learning from epidemiological analyses
- S103 EP05 Person-centred care: the advantages and challenges
- S109 EP06 TB: data matters
- S113 EP07 Improving TB care in children
- S118 EP08 COVID-19 and TB: friends or foes?
- S121 EP09 Improved acceptability of TB regimens needed
- S127 EP10 Overcoming barriers in the contact cascade of care

**ABSTRACT PRESENTATIONS  
THURSDAY, 22 OCTOBER 2020**

**ORAL ABSTRACT SESSIONS**

- S133 OA-10 Partnerships for integrating services
- S137 OA-11 New solutions to old TB challenges
- S140 OA-12 Confronting TB stigma
- S144 OA-13 The race for improved multidrug-resistant care
- S149 OA-14 COVID-19: the great disrupter
- S153 OA-15 TB preventive therapy: we need to do better
- S156 OA-16 TB Xpert in low- and middle-income countries: ensuring quality and quantity
- S160 OA-17 Safety first: side effects of old and new drugs
- S164 OA-18 (Im)possible mission: TB care in low-resourced settings
- S168 OA-19 Histories of success: improving TB and latent TB infection care
- S171 OA-21 Finding missing people with TB: targeted approaches

**E-POSTER SESSIONS**

- S176 EP11 TB: HIV and diabetes comorbidities
- S181 EP12 Approaches to paediatric TB prevention, diagnosis and treatment
- S187 EP13 Improving all steps of the TB cascade of care: from identification to beyond treatment
- S193 EP14 Reaching the hard-to-reach ones: strategies to overcome the challenges
- S198 EP15 All hands on deck: key stakeholders take initiative to end TB
- S205 EP16 TB: new insights on cost and cost-effectiveness
- S212 EP17 Facing TB during the COVID-19 pandemic
- S215 EP18 Scaling up TB preventive therapy: it is about time!
- S220 EP19 Quality and modelling of TB

**ABSTRACT PRESENTATIONS**  
**FRIDAY, 23 OCTOBER 2020**

**ORAL ABSTRACT SESSIONS**

- S226 OA-22 Improving the quality of care
- S230 OA-23 TB: finding the missing millions
- S234 OA-24 TB and diabetes
- S239 OA-25 TB: deep into molecular structure
- S242 OA-26 Using digital technology for TB elimination
- S245 OA-27 The social impact of TB in Europe
- S249 OA-28 New and old tests for latent TB infection
- S253 OA-29 Who pays the cheque? The economic burden of TB
- S258 OA-31 TB epidemiology

**E-POSTER SESSIONS**

- S263 EP20 Community healthcare workers in evidence
- S268 EP21 TB as an occupational hazard
- S273 EP22 TB adherence to treatment
- S280 EP23 TB in children and adolescents
- S283 EP24 TB innovative strategies to find the missing cases
- S289 EP25 Lung health across the lifespan
- S294 EP26 Improving knowledge: the benefits for person-centred TB care
- S299 EP27 Difficult problems in TB infection and treatment
- S304 EP28 Making the most of short money to fight TB

**ABSTRACT PRESENTATIONS**  
**SATURDAY, 24 OCTOBER 2020**

**ORAL ABSTRACT SESSIONS**

- S311 OA-32 Reaching the most vulnerable
- S314 OA-33 Overcoming impediments in tobacco control
- S317 OA-34 Risk factors, surveillance and control strategies in potential zoonotic TB hotspots
- S320 OA-35 New and existing TB drug resistance
- S325 OA-36 The role of pharmacies in the TB cascade of care
- S329 OA-37 TB and HIV potpourri
- S333 OA-38 Diagnostic assays quality and accuracy
- S237 OA-40 Health and well-being post-TB
- S340 OA-41 TB detection and treatment in mothers and children

**E-POSTER SESSIONS**

- S345 EP29 The European TB experience
- S349 EP30 Where are the undiagnosed TB cases?
- S355 EP31 Allied against TB: new and old partners
- S360 EP32 Quality improvement of the TB cascade of care
- S365 EP33 Barriers in the TB care cascade: it's time for local solutions
- S371 EP34 TB: from bench to the bedside
- S377 EP35 Ongoing battle against the tobacco industry
- S382 EP36 Molecular testing for TB infection and drug resistance
- S387 EP37 Joining efforts for TB elimination: the role of the private sector

## LATE-BREAKER PRESENTATIONS

### WEDNESDAY, 21 OCTOBER 2020

S393 OA-08 The Union student late-breaker session on lung health

### THURSDAY, 22 OCTOBER 2020

S397 OA-20 The Union late-breaker session on COVID-19

### FRIDAY, 23 OCTOBER 2020

S401 OA-30 The HIV-TB and diabetes late-breaker session

### SATURDAY, 24 OCTOBER 2020

S404 OA-39 The Union/CDC late-breaker session on TB

## SATURDAY, 24 OCTOBER 2020

S416 TBS4B Innovations in TB therapeutics: oral abstract presentations

### WEDNESDAY, 21 OCTOBER 2020 - SATURDAY, 24 OCTOBER 2020

S419 EPTBS TBScience 2020 - E-posters

S461 **Author Index**

## TBSCIENCE PRESENTATIONS TBScience Oral Abstract-Driven Presentations

### WEDNESDAY, 21 OCTOBER 2020

S409 TBS1B Role of innate and adaptive immunity in TB and evaluation of immune correlates in pre-clinical and clinical studies: oral abstract presentations

### THURSDAY, 22 OCTOBER 2020

S412 TBS2B Bacterial metabolic activity and the host response in TB disease: oral abstract presentations

### FRIDAY, 23 OCTOBER 2020

S414 TBS3B Latest research in drug resistance detection, mechanism and treatments: oral abstract presentations

# The International Journal of Tuberculosis and Lung Disease

*The Official Journal of the International Union Against Tuberculosis and Lung Disease*

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# 51st World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) Virtual event, 20 October – 24 October 2020

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## SYMPOSIA: WEDNESDAY 21 OCTOBER 2020

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### **SP-01 Strengthening evidence on optimal treatments for multidrug-resistant TB: approaches to studying timing and duration.**

#### **Follow-up duration in study of treatment of different durations: bias and implications**

G Davies,<sup>1</sup> <sup>1</sup>University of Liverpool, Liverpool, United Kingdom. e-mail: gdavies@liverpool.ac.uk

A major concern about shortened regimens is possible increased recurrence (relapse and reinfection) after treatment completion. Documented, systematic post-treatment follow-up is critical to accurately assess efficacy of shortened regimens compared to longer control regimens.

Failure to systematically follow patients in observational or experimental studies can result in underestimated recurrence after shortened regimens. Follow-up time for equivalent durations after treatment completion (e.g., 6 months after a 9-month regimen and after an 18-month control) can result in the same overestimate, which can bias the effect estimate. For that reason, guidance recommends defining total follow-up duration from the point of randomization, e.g., 24 months after randomization.

Effectively, this results in 15 months post-treatment follow-up for a 9-month regimen and 6 months for an 18-month regimen. This could overestimate recurrence in shortened regimens relative to controls and lead to bias. This talk will explore these biases and their implications for guidelines and programmatic decision-making.

### **Short, long, or somewhere in between? Designing clinical trials to identify the optimal duration of therapy**

P Phillips,<sup>1</sup> <sup>1</sup>University of California, San Francisco, San Francisco, United States. e-mail: Patrick.Phillips@ucsf.edu

Clinical development of new regimens for the treatment of TB involves not only the selection of the right drugs and doses, but also a choice of the optimal duration of therapy that maximizes efficacy while not exposing patients to a longer duration of potentially toxic drugs than necessary.

Different approaches have been considered to generate evidence to support this choice with varying success. Bedaquiline and delamanid have been evaluated in clinical trials and approved for the treatment of TB, but we are still learning the optimal duration of each.

In this presentation, I will talk about the latest clinical trial designs that are being applied in DS-TB and DR-TB randomized trials to efficiently identify optimal durations of new regimens. I will talk about the duration-randomized design which involves modelling of the duration-response relationship, proving a case study of how this has been applied in a planned TB trial.

### **Does prolonged use of bedaquiline improve treatment outcomes? An application of methods to study optimal treatment duration using observational data.**

M Franke,<sup>1</sup> <sup>1</sup>Harvard Medical School, Boston, United States. e-mail: molly\_franke@hms.harvard.edu

In observational research, a common approach to studying the effect of treatment duration entails categorizing patients according to the duration of their regimen (e.g., <15 months; 15-20 months, >20 months) and comparing the frequency of treatment success in patients with longer and shorter regimens.

Results derived from this approach may be biased in favor of longer treatment because patients who survive longer can receive longer treatment. On the other hand, results may be biased against longer treatment if patients receive longer treatments due to a slower treatment response or treatment-emergent toxicities that lim-

ited subsequent treatment options. To overcome these potential biases, we employ an alternative approach that emulates a randomized trial in which each individual is randomly assigned to a treatment duration.

We provide an illustrative example in which we compare the effects of bedaquiline for 24 weeks, 48 weeks or the entire duration of treatment on end-of-treatment outcomes.

### **Methodological challenges in analysis and reporting of sputum culture conversion endpoints in observational treatment cohorts**

C Rodriguez,<sup>1</sup> <sup>1</sup>Harvard Medical School, Boston, United States. e-mail: carly\_rodriguez@hms.harvard.edu

In observational MDR-TB treatment cohorts, time-to-sputum culture conversion (SCC) or SCC at specified time-points since treatment initiation (e.g. 6 months) are commonly used as interim endpoints for end-of-treatment outcome.

While World Health Organization definitions for SCC exist, there is substantial heterogeneity in how these definitions are operationalized given varying data collection practices, monitoring schedules, and laboratory procedures across cohorts.

We will discuss the potential for selection bias due to the use of prolonged periods to establish patients' baseline culture in SCC cohorts. We will describe the current state defining baseline sputum culture in the literature and recommend best practices for avoiding or resolving this bias.

### **How best to analyse and report adverse events occurring during MDR-TB treatment?**

M Bastard,<sup>1</sup> <sup>1</sup>Epicentre, Geneva, Switzerland. e-mail: Mathieu.BASTARD@geneva.msf.org

Is the new regimen safe? This is a priority question in the evaluation of new MDR-TB regimens. Adverse events reporting is critical to evaluate regimen safety.

However, drawing conclusions from observational adverse event data is challenging in the context of dynamic regimens. Important considerations include causality attribution in the context of regimens with multiple drug stops and starts; determining the dates of event onset and drug exposure; and adverse event recurrences.

In this talk, we will detail methodological challenges to the analyses and reporting of adverse event data and provide illustrative examples using data from the endTB observational study.

### **SP-02 Tests for the detection of TB infection - tuberculin skin test vs interferon-gamma release assays**

#### **Evidence and policy recommendations for testing for TB infection before TB preventive treatment**

Y Hamada,<sup>1</sup> <sup>1</sup>University College London, London, United Kingdom. e-mail: yohei.hamada0@gmail.com

Tuberculosis Preventive Treatment should be selectively targeted to population groups at highest risk of progression to active disease. WHO guidelines strongly recommend TPT for adults and adolescents living with HIV, and children aged <5 years who are household contacts of people with bacteriologically confirmed pulmonary TB, if active TB is excluded.

These groups should be given TPT even if TB infection testing is unavailable. However, for household contacts aged  $\geq$  5 years, confirmation of TB infection using IGRA or TST before starting TPT is desirable.

Finally, systematic testing for TB infection and TPT is recommended for people who are initiating anti-TNF treatment, receiving dialysis, preparing for an organ or haematological transplant, or who have silicosis, and may be done for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs. In this presentation the WHO recommendations and underlying evidence are discussed.

#### **TST vs IGRA**

D Cirillo,<sup>1</sup> <sup>1</sup>San Raffaele Scientific Institute, Milano, Italy. e-mail: cirillo.daniela@hsr.it

Currently available tests for TB infection have major limitations. They have poor predictive value for development of active TB and do not indicate whether treatment of TB infection has been successful, which means that most persons who have successfully completed what is considered an adequate course of preventive treatment will usually continue to have a positive test.

IGRA needs sophisticated laboratory infrastructure and technical expertise, and expensive equipment. TST is considered less resource intensive than IGRA but it requires a cold chain, two health care visits and needs training for intradermal injection, reading and interpretation and its quality control is a challenge.

In the following presentations we present the true differences in the performance of these tests, but also the different roles these tests have in different settings.

## Supplies of TST/IGRA

B Waning,<sup>1</sup> <sup>1</sup>Stop TB Partnership, Geneva, Switzerland.  
e-mail: brendaw@stoptb.org

Governments and donors should invest and build health system capacity (human resources, logistics and supply chain and M&E) for TST and/or IGRA to avoid unnecessary TPT and related harms and improve acceptance. For TST this enquires ensuring the availability and supply of tuberculin in cold chain as well as syringes, needles and consumables.

IGRA tests have many infrastructural requirements (e.g. capacity of the laboratory system to conduct IGRA including phlebotomy, processing of blood specimen, incubation and enzyme-linked immunosorbent assay (ELISA) reading) and are costly (unit test costs as well as need for laboratory infrastructure and laboratory personnel), making routine programmatic use in most LMICs challenging. Supply of appropriate reagents and testing tubes for IGRA need to be ensured.

However, having this capacity in place will also enable rapid adoption of any new TB infection test endorsed for programmatic use in future.

## Future tests for TB infection

M Ruhwald,<sup>1</sup> <sup>1</sup>Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland.  
e-mail: morten.ruhwald@finddx.org

New versions of TST and IGRA are expected to be launched in the immediate future, all using recombinant ESAT6-CFP10 antigens (C-Tb (Serum Institute of India, India), Diaskin Test (Generium, Russian Federation) and ESAT6-CFP10 test (Anhui Zhifei Longcom, China)) as well as point of care IGRA tests (Quantiferon Access and Standard E and F TB-feron tests from SD biosensor and the Advansure TB-IGRA test from LG Chem).

Qiagen and SD Biosensor have both developed a simplified version of the IGRA that can be operated in peripheral facilities without laboratory infrastructures. These tests offer an incremental gain in ease of use or cost or other operational aspects but are not expected to provide major advantages in diagnostic test accuracy or predictive ability.

In this presentation the status of development of new tests is presented, potential advantages and disadvantage of future tests for TB infection are discussed and remaining gaps are identified.

## SP-03 When novel product bans are best: lessons learned and challenges faced in tackling tobacco in low-and middle-income countries.

### Mexico: Industry Attempts to Influence Government

I Barrientos-Gutierrez,<sup>1</sup> <sup>1</sup>National Institute of Public Health, Mexico City, Mexico. e-mail: inti.barrientos@insp.mx

Since its latest iteration, stemming from the 2003 patent, vaping has transformed from a hobbyist movement to a rapidly growing industry. Headed by the big tobacco companies, along with the new specialized companies and “users” groups, this new industry is not shy about using all the tools developed by the tobacco companies to achieve a legal and social situation that favors their interests.

A prolific marketing effort, legal trials, alliances with legislators, sponsored scientific articles, news and media inserts, and public attacks on those who do not share their position are just some of the methods used, magnified through the use of social networks.

In Mexico these efforts has been stronger in the last two years, since the ban turned 10 years of being imposed, and the products of large tobacco companies (BAT's Vype and PMI's IQOS) have been illegally introduced to the Mexican market.

### Vietnam: Working Towards Legislation on ENDS and HTPs

T Linh,<sup>1</sup> <sup>1</sup>Vietnam Tobacco Control Fund, Ha Noi, Vietnam.  
e-mail: thuylinh.vinacosh@gmail.com

This session will outline current state of the legislation in Vietnam, including timeline and progress of revising Decree 67. It will also identify:

- Some barriers and opinions on ENDS & HTPs of agencies and enterprises
- Opinion of Ministry of Health and orientation of legislation in Vietnam.

## Reflections on the One Year Anniversary of the Ban

L Swasticharan,<sup>1</sup> <sup>1</sup>Ministry of health and Family Welfare, New Delhi, India. e-mail: drswasti@yahoo.com

In September 2019, India announced a federal ban on the production, import and sale of e-cigarettes, noting that these products are harmful to health. This session will describe decisions and factors leading to the ban and outline any issues that emerged—either in support of or in opposition to the ban. It will also describe progress and challenges faced over the year-long period since the ban was announced and detail goals for the next year.

## SP-04 Advancing TB prevention in children during the COVID-19 pandemic

### Overview of TB prevention services in children and adolescents

A Brands,<sup>1</sup> <sup>1</sup>WHO, Geneva, Switzerland. e-mail: brandsa@who.int

In this talk, we will present a policy overview and coverage of TB prevention services among eligible children and adolescents.

We will share reports from regional and country colleagues as well as partner organizations on the effect of COVID-19 on TB prevention services.

### The effect of COVID-19 on childhood TB preventive treatment services in sub-Saharan Africa: experiences from Cap TB project

M Casenghi,<sup>1</sup> <sup>1</sup>Elizabeth Glaser Pediatric AIDS Foundation, Geneva, Switzerland. e-mail: mcasenghi@pedaids.org

Contact Investigation and delivery of TB Preventive treatment (TPT) are WHO-recommended core components of childhood TB programming. Between Q4 2018 and Q1 2020, the CaP TB project has supported facility-based implementation of those interventions in purposively selected sites across nine African countries. As of March 2020, project countries have started enforcing measures aimed at controlling the COVID-19 pandemic, with repercussions on accessibility to health services that varied among countries.

This presentation will discuss the effect of COVID-19 control measures and interventions on delivery and accessibility of contact investigations and TPT services, as documented by key patient level indicators collected through the project framework for monitoring and evaluation. It will also discuss the effectiveness and feasi-

bility of mitigation measures introduced to ensure continuation of those essential TB prevention services in the context of the COVID-19 pandemic.

### Impact of COVID-19 on 3HP rollout: Experiences from IMPAACT4TB

N Salazar-Austin,<sup>1</sup> <sup>1</sup>Johns Hopkins School of Medicine, Baltimore, United States. e-mail: nsalaza1@jhmi.edu

Provision of TB preventive therapy to household child contacts and people living with HIV is key component of the END TB Strategy. The IMPAACT4TB Project was scheduled to begin roll out of 3HP, a new short-course TB preventive therapy regimen, in 12 high burden countries in March 2020 as the COVID-19 pandemic was beginning to unfold. As countries developed their COVID response, there have been large ramifications for healthcare delivery including contact investigations and TB prevention services.

We will discuss mitigation measures and alternative models of care that have been implemented to ensure these services have continued during the COVID-19 pandemic response.

### Flexible child contact management framework

Y Hirsch-Moverman,<sup>1</sup> <sup>1</sup>ICAP at Columbia University, New York, United States. e-mail: yh154@columbia.edu

The WHO roadmap for childhood TB recommends an ‘integrated, family and community-centered strategy’. Yet, there is no clear guidance on how health systems can operationalize such a strategy. It is crucial to recognize that barriers that impede successful child contact management (CCM) vary from family to family, even within the same community. COVID-19 further complicates delivery of CCM during the pandemic and recovery periods.

We propose a flexible CCM framework, which goes beyond standardized approaches. Suggestions will be provided on how health systems could support a framework that is customized for each child’s/family’s needs as well as their varied environments.



## SP-05 Updating World Health Organization TB screening guidelines: evidence reviews of the yield, tools and costs of screening.

### Overview and systematic review of the number needed to screen for active TB

L Chaisson,<sup>1</sup> <sup>1</sup>University of Illinois at Chicago, Chicago, United States. e-mail: lchais@uic.edu

One of the pillars of the WHO End TB Strategy is to increase early diagnosis of TB through implementing systematic screening programs for high-risk groups. Active case finding (ACF) is a useful tool for targeted screening, and has been shown to reduce time to TB detection, TB incidence, and mortality. This presentation will review results of a systematic review undertaken to evaluate and synthesize the existing body of evidence that has been collected about ACF to assess the number needed to screen (NNS) in order to detect one case of active TB.

Specific outcomes assessed include:

- 1) the average NNS in order to detect one case of active TB,
- 2) the average NNS for high-risk groups (including prisoners, pregnant women, persons with diabetes, drug users, healthcare workers, and others, and;
- 3) how different screening tools (including symptom screening, CXR, Xpert, and others) affect NNS.

### Performance of symptoms and chest radiography as screening tools and choosing algorithms for screening for active TB

A van't Hoog,<sup>1</sup> <sup>1</sup>Amsterdam University Medical Center, Department of Global Health, Amsterdam, Netherlands. e-mail: a.h.vanhoog@aighd.org

The accuracy of screening tools, in combination with confirmatory testing, determines the performance and yield of a screening program and the burden on individuals and the health service. Symptom questioning and chest radiography (CXR) have been the most widely available screening tools used to date.

We conducted a systematic review to assess the sensitivity and specificity of symptom screening and chest radiography for detecting bacteriologically-confirmed active pulmonary TB, assessing potential sources of heterogeneity. To inform disease control programs about the choice of appropriate screening and diagnostic tools for tuberculosis screening, we compared the performance of a range of screening algorithms in decision analytical models, assessing the yield, number needed to screen (NNS), positive predictive value (PPV), and resource implications (cost per true case detected and individual screened) for different TB epidemiological and population settings.

## Computer Aided Detection (CAD) Solutions for Pulmonary Tuberculosis: what is their performance in screening and diagnostic triage settings?

S Kik,<sup>1</sup> <sup>1</sup>Foundation for Innovative New Diagnostics, The Hague, Netherlands. e-mail: Sandra.Kik@finddx.org

The TB field welcomed several computer aided detection (CAD) products that provide an automated, standardized interpretation of a digital chest x-ray (CXR). CADs generate an abnormality score that can be used to identify individuals requiring further diagnostic testing.

FIND established an archive of CXRs from various data sources with representation of different geographical origin, high and low TB risk groups from screening and triage settings. The archive, housed at an offline facility, contains images that were not used for training of any of the CADs and is used to assess the accuracy of CAD4TB (Delft Imaging), Lunit Insight CXR (Lunit Insight) and qXR (Qure.ai) for their ability to detecting pulmonary abnormalities suggestive of TB compared against a microbiological, human radiologist and composite reference standard.

In this talk, accuracy is presented for each CAD and the consequences for their use as screening or triage tool will be discussed.

## Screening tests for active pulmonary tuberculosis in children—A systematic review

B Vonasek,<sup>1</sup> <sup>1</sup>University of Wisconsin School of Medicine and Public Health, Madison, United States. e-mail: vonasek@wisc.edu

Case finding is a crucial step in the cascade of care for patients with TB, however in many children the disease is never diagnosed. National and international recommendations for child health generally lack guidance on systematic screening strategies for TB.

This presentation will share findings from a recently conducted systematic review and meta-analysis assessing the accuracy of several screening strategies for child TB, including various symptoms and symptom combinations, chest radiography, Xpert MTB/RIF, Xpert Ultra, and combinations of these tests.

This review focuses on screening of children and adolescents up to 19 years old in high-risk groups, including contacts of persons with TB, children living with HIV, and children with pneumonia) of children. Implications of these findings will be discussed.

### Costs and cost-effectiveness of TB screening – A systematic review

H Alsdurf,<sup>1</sup> <sup>1</sup>University of Ottawa, Ottawa, Canada.  
e-mail: halsdurf@uottawa.ca

The presentation will include key results from a systematic review of the published literature on economic evaluations for TB screening including active and intensified case finding with a particular focus on the following tools: Symptom screens (prolonged cough and any symptom), Chest X-ray (CXR) and CXR using automated detection such as CAD4TB, and GeneXpert MTB/RIF and Xpert Ultra. We included studies that compared these TB screening approaches to standard case detection and looked at study outcomes including numbers of cases detected and impact on TB epidemiology in a community.

We will present current economic evidence and key costs, cost-effectiveness results and discuss affordability of these screening approaches. We will also present results among high-risk populations, such as people living with HIV, migrants, prisoners and people with diabetes.

### SP-06 The people-centred framework for national and subnational TB planning and programming: early adopters share lessons learned and experiences

#### Using the People-Centred Framework for NSP development while on lock-down due to COVID-19

P Migambi,<sup>1</sup> <sup>1</sup>Rwanda Biomedical Centre (RBC), Kigali, Rwanda. e-mail: patrick.migambi@rbc.gov.rw

The COVID-19 pandemic and lockdown to mitigate spread impacted the finalization of the NSP and development of the NSP-based TB & HIV combined Global Fund Funding Request.

Under unprecedented circumstances, how did Rwanda manage to adopt the People-Centred Framework (PCF), data consolidation and visualisation along the care continuum and TIME modelling to support prioritisation and optimisation, before the lockdown? And a Patient Pathway Analysis to assess the alignment of care-seeking and service availability, with distant support from consultants due to international travel restrictions? The intervention package scenarios to compare budget to best impact and the GFFR development, with a mix of in-country and distant TA?

Patrick Migambi will share challenges, experiences, creative solutions and lessons-learned.

### Developing an evidence-informed NSP using epidemiological, people-centred and systems-related data

S Turyahabwe,<sup>1</sup> <sup>1</sup>Kampala, Kampala, Uganda.  
e-mail: turyahabwestavia@gmail.com

Uganda is one of the early adopter and approach shaper countries for the People-Centred Framework for TB programming. The development of the Uganda national TB strategic plan (2020/21-2024/5) employed a patient-centred approach and was informed by the evidence gathered through a data consolidation process along the TB care continuum.

The process included a patient pathway analysis (PPA) that was carried out to assess the alignment between country-level service provision and initial care-seeking by the population. Data was consolidated into an excel tool with automated data visualizations based on key performance indicators that provided evidence on epidemiology, people and systems.

The evidence generated provided a basis for problem identification, prioritisation; root cause analysis, intervention identification and optimisation.

### Developing an optimized NSP using TIME Impact & TIME Economics

T Letta,<sup>1</sup> <sup>1</sup>Ministry of Health, Federal Democratic Republic Ethiopia, Addis Abeba, Ethiopia.  
e-mail: tayeletta@gmail.com

Ethiopia, under the now-ending national TB strategic plan, has made significant strides to achieve the End-TB goals. By the end of 2018, 96% of public hospitals and health centres; 71% of private hospitals; 6.5% of private specialized clinics; and 22% of private medium clinics were providing TB diagnostic and/or treatment services. However, the country still remains among the top 30 high TB, TB/HIV and MDR-TB burden countries, and over a third of estimated 165,000 TB cases were missed in 2018. The country's TB program had about 60% funding gap in 2018.

In an effort to address the remaining challenges, we analyzed policy, programmatic and implementation gaps and did root-cause analyses using the people-centred framework (PCF). We combined our in-house modelling capacity with support from external consultants to develop an optimized NSP.

We share our experience with the PCF approach with particular focus on TIME Impact and TIME Economics modelling.

## SP-07 Towards new TB vaccines: progress and considerations for introduction

### WHO Preferred Product Characteristics for Preventive and Therapeutic Vaccines

A Ginsberg,<sup>1</sup> <sup>1</sup>Bill and Melinda Gates Foundation, Washington DC, United States.  
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This presentation outlines WHO's preferred and minimal product characteristics (PPCs) for both preventive and therapeutic vaccines. These PPCs intend to articulate attributes of products that are suitable for end users, to scientists, funding agencies and industry groups developing TB vaccine candidates intended for WHO prequalification and policy recommendations.

### The clinical development pipeline of new TB vaccines

D Tait,<sup>1</sup> <sup>1</sup>IAVI, Cape Town, South Africa.  
e-mail: dtait@iavi.org

This presentation will summarize the progress in the clinical development pipeline of new TB vaccines, and the prospect for their availability and use in countries that need them most.

Considering that vaccines potentially offer a novel approach to combat emergence and transmission of anti-TB resistance, this session will also seek to inform the debate on the use of new vaccines in settings with high level of resistance.

### A global roadmap for the research and development of new TB vaccines

F Cobelens,<sup>1</sup> <sup>1</sup>University of Amsterdam, Amsterdam, Netherlands. e-mail: f.cobelens@aighd.org

This presentation will share findings from the development of a global roadmap for the research and development of new tuberculosis vaccines, which was launched in 2020. The roadmap articulates elements of need across the clinical development, delivery and implementation of new TB vaccines in the form of research questions, as well as capacity needs with an end-to-end perspective. Crosscutting challenges and opportunities at the scientific, financial, policy, regulatory, manufacturing and access interface will be discussed in this presentation.

## Assessing the full value of new TB vaccines for decision-making

R White,<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
e-mail: Richard.White@lshtm.ac.uk

The introduction of a new vaccine into national immunisation programmes often involves a trade off with investing in other vaccines or alternative strategies. As such, countries need broader information for assessing the comparative health and economic impact of new vaccines before implementation.

I will share an update on progress in a project designed to assess the potential health and economic impact of new tuberculosis (TB) vaccines, using various vaccine characteristics and implementation scenarios.

The intended goal is to proactively prepare evidence necessary for decision-making by countries, partners and institutions involved in new TB vaccine development and implementation.

## SP-08 Incarceration for drug use and TB among people who use drugs – time to break the cycle

### Incarceration, drug policies and tuberculosis in Tanzania and across Africa: reflections by the community of people who use drugs

H Assan,<sup>1</sup> <sup>1</sup>Tanzanian Network of People Who Use Drugs, Dar es Salaam, Tanzania, United Republic of.  
e-mail: happy.assan@gmail.com

In her presentation Happy will reflect about impact of incarceration and drug policies on tuberculosis in Tanzania and across Africa, particularly among women who use drugs. She will also share information about the situation with tuberculosis and MDR tuberculosis, including among the key populations, in the Tanzania. She will share what concerns her most and what gives her hope for the way forward.

### The heavy toll of drug policies on tuberculosis: prison health and human rights

C Daniels,<sup>1</sup> <sup>1</sup>Harm Reduction International (HRI), NA, South Africa. e-mail: Colleen.Daniels@hri.global

Colleen Daniels will present an overview and discuss that prisons are a highly ineffective way to deal with people who use drugs. With incarceration rates increasing every year, bad living conditions in prisons exacerbated by poor access to healthcare jeopardizes the fight against communicable diseases, particularly tuberculosis.

The presentation will discuss how mass incarceration, overcrowded prisons, and human rights violations contribute to fueling tuberculosis. These issues are compounded in countries that have high rates of incarceration for drug-related offences, and in settings where there is no continuity of treatment for people entering and leaving the prison system.

With a global prison population of 11 million people that keeps increasing every year, many prisons in the world are overcrowded due to the incarceration of people for drug-related offences, over 80% of them are in prisons for non violent offences. In some countries, over 50% of the prison population are held under drug-related offences, while among female inmates this proportion is higher and up to 80% in some countries.

This presentation will outline the need to reform drug policy as an effective approach to fight tuberculosis and HIV.

### **Reflections and suggestions for the way forward from people who use drugs in Asia**

Y Jonet,<sup>1</sup> <sup>1</sup>Malaysian AIDS Council, Kuala Lumpur, Malaysia. e-mail: contactus@mac.org.my

Tuberculosis is one of the fastest growing epidemics among prison populations and one of the main causes of death, particularly in low- and middle-income countries. Yatie Jonet will share cross-Asia perspectives of people who use drugs on the influence of criminalization on health, with a focus on tuberculosis. She will share powerful stories about experiences of people who use drugs with incarceration: getting infected in prison, lacking treatment in prison as well as positive stories on access to treatment in prison! She will share suggestions on the way forward from people who use drugs, focusing on needs of women who use drugs. She will share what concerns her most and what gives her hope for the way forward.

### **COVID-19, tuberculosis, harm reduction and prisons: challenges and opportunities'**

L Yarcia,<sup>1</sup> <sup>1</sup>No Box Transitions Foundation, Manila, Philippines. e-mail: Leeyarcia@nobox.ph

Lee will reflect on his personal journey of being the lawyer and the doctor. He will also share information about the situation with tuberculosis and MDR tuberculosis, including among the key populations, in the Philippines. Prisons and other closed settings are high risk environments for communicable diseases such as HIV, hepatitis C, tuberculosis as well as COVID-19. This presentations will draw on experiences in the Philippines. It will discuss that prisons, drug use and HIV are all independent risk factors for the development of tuberculosis and amplify each other into synergistic comorbid phenomena. In the current context, COVID-19 also puts detained

people and prison staff at extremely high risk, on top of these existing health threats. Yet the COVID-19 pandemic has also prompted countries to release people who were incarcerated for non-violent offences, including people who use drugs.

This approach should urgently be adopted in other countries too and critically, it opens up a debate about whether people who use drugs have rightly been detained in the first place.

### **Vision, evidence and roadmap for the way forward**

M Kazatchkine,<sup>1</sup> <sup>1</sup>The Global Commission on Drug Policy, Geneva, Switzerland.  
e-mail: contact@michelkazatchkine.com

Professor Michel Kazatchkine will discuss that punitive approaches to drug use and repressive drug policies have been hindering the results of the investments made in the fight against communicable diseases, particularly tuberculosis, with health outcomes exacerbated by overcrowding and unhealthy conditions, particularly in Eastern Europe and Central Asia. Michel will discuss how UN bodies and other regional human rights monitors could be better at monitoring and reporting on the issue of tuberculosis in prisons.

Building on data related to incarceration around the world this presentation will reflect that political will and partnerships, including with the medical, scientific communities and decision makers, including parliamentarians and city mayors, are the main driver for drug policy reform and effective response to tuberculosis and co-infection; and mobilization of the community working on addressing tuberculosis is key for scale up of harm reduction services and drug policy reforms. It will discuss that further progressing drug policy reform across countries is key for the effective response to tuberculosis.

The presentation will discuss the impact of over incarceration on the achievement of the HLM on tuberculosis targets, discuss solutions and suggested way forward and will reflect on the presentations made.

### **SP-09 Ending TB in vulnerable populations through operational research, capacity building and evidence-informed decision making in Eastern Europe and Central Asia (Find-Treat-All).**

#### **Scale-up and impact of an electronic medical record system (Open MRS) and GxAlert on diagnosis of TB and linkage to treatment in Tajikistan**

S Khushvakhtov,<sup>1</sup> <sup>1</sup>Republican Centre for Protection of Population from Tuberculosis in Tajikistan, Dushanbe, Tajikistan. e-mail: kh.shodmon@gmail.com

The advent of the automated Xpert MTB/RIF assay has so far failed to speed up time between diagnosis and treatment of tuberculosis (TB), mainly because of the need for personnel and paper-based interfaces to link results with TB registers. GxAlert is an electronic data monitoring system that automatically connects Xpert instruments to the network and mobile channels to communicate assay results. This should lead to patients being diagnosed and initiated on treatment more quickly. Tajikistan started scaling up GeneXpert instruments in 2014. From 2017 these instruments were connected to GxAlert. During this period, the country scaled up a new Open MRS medical information system allowing more reliable recording and reporting of TB control efforts.

This study presents the scale-up and national coverage of GeneXpert / GxAlert and Open MRS in Tajikistan between 2014 and 2019 and the impact of this on TB diagnosis and timely linkages between diagnosis and treatment.

#### **Outcomes of video observed TB treatment (VOT) for drug-susceptible TB in the Republic of Moldova**

S Doltu,<sup>1</sup> <sup>1</sup>AFI, Chisinau, Moldova, Republic of. e-mail: svetlana.doltu@gmail.com

Asynchronous Video observed treatment (aVOT) has been proposed as an alternative method of ensuring medication adherence in tuberculosis (TB) patients compared with directly observed therapy (DOT). Current study used 2016-2017 secondary data from the Randomized Clinical Trial (RCT) piloted aVOT Strategy in Chisinau and data from national TB register. From 647 TB patients included in the study, 169 were from RCT group (83 – in aVOT and 86 – in DOT) and 478 – DOT in practical conditions (control group).

Based on the suggestions of the parent study aVOT may be an acceptable approach to treatment monitoring, our supplementary results show that aVOT was superior to

DOT in terms of treatment outcomes as well; aVOT was associated with short- and long-term TB treatment favourable outcomes. aVOT as a new patient-centred approach improving treatment adherence and outcomes might be recommended as an alternative to DOT strategy in the Republic of Moldova.

#### **People Who Inject Drugs in Ukraine: comparative analysis of tuberculosis treatment outcomes in relation to Opioid Substitution Therapy**

T Fomenko,<sup>1</sup> <sup>1</sup>Alliance for Public Health, Kyiv, Ukraine. e-mail: fomenko@aph.org.ua

People Who use Injectable Drugs (PWID), who are often socially marginalised and have limited access to health services, are at high risk of being infected with Mycobacterium tuberculosis and developing tuberculosis (TB). Many PWID are also infected with HIV and hepatitis C. Opioid substitution therapy (OST – using methadone or buprenorphine) is one of the pillars of harm reduction strategies for PWID and should be an integral part of TB care.

In Ukraine, the Alliance for Public Health coordinates TB and HIV prevention and care services for PWID and has integrated a model of “OST with TB care at the same facility”. Between July 2017 and July 2019, there were 200 PWID diagnosed with TB in five large regions of Ukraine.

The current study documented numbers on OST, socio-demographic and clinical characteristics of those on and off OST and treatment outcomes in relation to OST, HIV status and hepatitis C.

#### **The effect of psychotherapy/psychiatric support for alcohol use disorder for Multi-Drug Resistant Tuberculosis in Zhytomyr, Ukraine**

V Plokykh,<sup>1</sup> <sup>1</sup>Medecins Sans Frontiers, Zhytomyr, Ukraine. e-mail: MSFOCB-Zhytomyr-Psychiatrist@brussels.msf.org

Ukraine is among the high burden countries for multi-drug-/rifampicin-resistant tuberculosis (MDR/RRTB). The country ranks in the top ten for years lost due to disability and premature mortality as a result of alcohol abuse, and TB control efforts are often adversely affected by alcohol use disorder (AUD).

Mental health interventions can be effective in reducing alcohol use and together with psychosocial support, these may improve patients' adherence to TB treatment and result in more favorable TB treatment outcomes. Of 73 patients with RR-TB in Zhytomyr region, Ukraine, 33 were screened positive for AUD and eligible for mental health interventions: 22 received this support and 11 declined.

This study compared the two groups with respect to socio-demographic and clinical characteristics, measures of depression, adherence to TB medications and interim / final TB treatment outcomes. The study also assessed why some patients declined to be helped.

### **SP-10 High-dose rifapentine with or without moxifloxacin for shortening treatment of TB: TB Trials Consortium Study 31/ACTG A5349 phase III clinical trial results**

#### **The design and primary efficacy results of Study 31/A5349**

S Dorman,<sup>1</sup> <sup>1</sup>Medical University of South Carolina, Charleston, United States. e-mail: dorman@musc.edu

In this talk the design and the efficacy results for Study 31/A5349, a randomized, open-label, controlled phase 3 trial, will be presented. The trial's primary efficacy endpoint is tuberculosis disease-free survival at twelve months after study treatment assignment. A total of 2,516 participants from 33 sites in 13 countries were enrolled. The proportion of participants who are culture negative at eight weeks and time to stable sputum culture conversion (on solid and liquid media) will also be reported.

#### **Safety of high-dose rifapentine regimens**

E Kurbatova,<sup>1</sup> <sup>1</sup>U.S. Centers for Disease Control and Prevention, Atlanta, United States. e-mail: ies3@cdc.gov

This talk will review safety data of the two high-dose rifapentine regimens. The proportion of participants with grade 3 or higher adverse events during study drug treatment will be described. Rates of discontinuation of assigned treatment for a reason other than microbiological ineligibility will be reported. All-cause mortality including all deaths from any cause during treatment or follow-up will be described with primary cause of death reported by the regimen.

The presentation will also include suggestions for safety monitoring and patient management for the short regimen in programmatic settings.

### **Secondary efficacy and safety analyses of short regimen performance by disease phenotypes and patient subgroups**

P Nahid,<sup>1</sup> <sup>1</sup>University of California, San Francisco, San Francisco, United States. e-mail: pnahid@ucsf.edu

Known risk factors for relapse and treatment failure include extensive cavitation, higher smear grade, low BMI and a compromised immune system because of HIV infection or uncontrolled diabetes.

This talk will review results of secondary analyses that further explore the efficacy and safety of the short regimens, highlighting particular groups of patients that experienced the most benefit.

### **Perspectives on shortened TB regimens: local medical and community views**

G Muzanye,<sup>1</sup> <sup>1</sup>Kampala, Kampala, Uganda. e-mail: gxm62@case.edu

This talk will focus on local medical and community perspectives considering the promise, value-add and possible challenges and solutions to implementation of short TB regimens. These will be considered in a specific country setting, contextualizing the findings.

### **Lessons learned and next steps**

R Chaisson,<sup>1</sup> <sup>1</sup>Johns Hopkins Center for Tuberculosis Research, Baltimore, United States. e-mail: rchaisson@jhmi.edu

This talk will discuss lessons about inclusion of adolescents and HIV-positive individuals with CD4 count threshold of 100 cell/mm<sup>3</sup>, adherence, regional differences, a novel "possible poor treatment response" process for endpoint ascertainment, and the value of standardized laboratory techniques. Relevant future actions will be considered.

## SP-11 Treating mild asthma: a paradigm shift

### 1. GINA 2019: A fundamental change in asthma management.

H Reddel,<sup>1</sup> <sup>1</sup>Woolcock Institute of Medical Research, The University of Sydney Chair, Global Initiative for Asthma (GINA), Sydney, Australia.  
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New recommendations about the treatment of mild asthma that were published by the Global Initiative for Asthma (GINA) in early 2019 have been described as the most fundamental change in asthma management in 30 years.

These recommendations represented the culmination of a decade-long campaign by GINA to develop new strategies for mild asthma with the aim of reducing asthma morbidity and mortality, particularly in low resource countries. They were prompted by concerns about the risks and consequences of treating mild asthma with short-acting beta<sub>2</sub>-agonists alone.

This presentation will describe the background to the changes, the evidence obtained from large new clinical trials and observational studies that provided the basis for the new GINA recommendations, the issues and priorities that were taken into account, and the global challenges and evidence gaps that remain.

### As-needed use of ICS and SABA in separate inhalers? Applicability to children.

L Garcia-Marcos,<sup>1</sup> <sup>1</sup>University of Murcia, Murcia, Spain.  
e-mail: lgmarcos@um.es

Description: One of the more frequent issues in difficult asthma in children is adherence. Using inhalers only when they are needed could be a good way to improve adherence and control.

This presentation would update the evidence on the efficacy of treating asthma in children using and as needed combination of short-acting beta-2 agonists and corticosteroids combined in the same inhaler as compared to the standard approach in GINA guidelines. If this approach is safe and effective in children, as being more affordable, should be seriously considered.

### Combination inhaler (ICS/ formoterol) Applicability to children: A Low resource setting perspective.

R Masekela,<sup>1</sup> <sup>1</sup>Head of Department of Paediatrics and Child Health, at the University of KwaZulu Natal, Durban, South Africa. e-mail: masekelar@ukzn.ac.za

Asthma in children is increasing in prevalence in children in low middle-income countries. Risk factors for this increase and poor asthma control in this population are poorly studied. One of the critical gaps in asthma treatment is access to affordable and safe medication delivered via an appropriate delivery system.

The current GINA recommendations encourage the use of combination therapy to improve asthma control, but this may not be possible in settings where there is poor access to spacer delivery systems and unaffordability of drugs.

Motivation for one drug device to manage asthma is an attractive option in this setting where there is an overuse of short-acting beta-agonist, together with interventions and advocacy to improve access to asthma treatment may be a solution to this issue in low-income settings.

### Obtaining optimal control of asthma in resource limited settings: theory and practice

C Chiang,<sup>1</sup> <sup>1</sup>Consultant at the International Union Against Tuberculosis and Lung Disease (The Union), Paris, France.  
e-mail: cychiang@theunion.org

The management of asthma requires medicines relaxing airway smooth muscles and reducing airway inflammation. Rapid-acting b<sub>2</sub> agonist does not effectively address the underlying problem of airway inflammation. Excess use of inhaled bronchodilators alone for symptom relief may result in a delay in seeking health care. Inhaled corticosteroid (ICS) is critical in the treatment of airway inflammation but is underused.

A substantial proportion of patients with persistent asthma in resource-limited settings have no access to affordable ICS for long-term treatment. Studies have shown that the use of both ICS and rapid-acting b-agonist as needed for symptom relief might be a better option.

## **SP-12 Scale-up of joint action on diabetes and TB – lessons from the field**

### **Global status on uptake of the Union/WHO Collaborative Framework for the Management of Tuberculosis and Diabetes**

A Baddeley,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: baddeleya@who.int

The Union/WHO Collaborative Framework for the Management of Tuberculosis and Diabetes was published in 2011. Whilst we have seen impressive scale-up of collaborative action on HIV-associated TB globally during this period, uptake and scale-up of collaborative TB and diabetes activities appears to have been limited and difficult to gauge.

This presentation will introduce the symposium and provide an overview of findings from a policy review conducted by WHO to assess uptake by high burden TB countries of the collaborative framework for the management of tuberculosis and diabetes and outline plans to promote further scale-up.

### **Addressing comorbidities as part of high impact TB interventions in Global Fund funding requests and grants**

M Yassin,<sup>1</sup> <sup>1</sup>The Global Fund, Geneva, Switzerland. e-mail: Mohammed.Yassin@theglobalfund.org

The presentation will share opportunities from the Global Fund to address comorbidity as one of the high impact interventions – this includes the Global Fund strategy and policy on supporting comorbidity, integrated services and promotion of innovations.

Further opportunities available through catalytic funding to support innovative interventions to find missing people with TB/DR-TB including among high risk groups such as people with diabetes.

Additional resources to address TB and comorbidity could be leveraged through existing country grants (savings and reprogramming), portfolio optimization and new grants.

### **Challenges, enablers and plans for scaling up integrated action on TB and diabetes: lessons from Pakistan**

A Quadir Baloch,<sup>1</sup> <sup>1</sup>National TB Control Programme, Islamabad, Pakistan. e-mail: draurangzaib@ntp.gov.pk

The dual burden of diabetes and TB is a serious and growing challenge for the poorly resourced health system of Pakistan which ranks 5th among the high TB burden countries. The number of diabetics are estimated to rise to 13.9 million by 2020 in Pakistan, increasing country ranking to 4th in the world.

This presentation will give an overview of studies that have been conducted to pilot bidirectional screening for diabetes in TB clinics and for TB in diabetes clinics. It will also discuss the challenges and barriers to integration at all levels of the health system and how the country plans to ensure integrated and structured bi-directional screening, referral, case management and follow-up is scaled up from 2020-2023.

### **Experience of initiating TB preventive treatment among people with diabetes in Brazil**

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The National TB Programme of Brazil has recently been introducing a policy on TB prevention among people with diabetes. This presentation will give an overview of the epidemiology of TB and diabetes in Brazil, common aspects and areas for synergy between the two programmes, Brazil's experience of introducing programmatic management of latent TB infection as well as preliminary results of TB preventive treatment in people affected by diabetes.

### **Introducing diabetes into TB/HIV collaboration: opportunities and plans for addressing multi-morbidity in Zimbabwe**

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Zimbabwe is one of the high tuberculosis burden countries with more than half of people with TB coinfecting with HIV. In 2017, the prevalence of diabetes among adults in Zimbabwe is estimated to be 1.8% and over 75.0% of those with diabetes had never been diagnosed.

This presentation will give an overview of the epidemiological background, and the steps taken to assess feasibility of implementation and to scale-up collaborative action on TB and diabetes in Zimbabwe. It will further discuss the challenges, enablers, opportunities and plans for national scale-up of integrated TB, diabetes and HIV care.



## SP-13 Deadly partners - COVID-19, non-communicable diseases and tobacco

### COVID-19, NCDs, and impact on young people

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Young people, especially those living with NCDs and its associated risk factors are vulnerable and susceptible to developing COVID-19 and its complications. This includes incomplete treatment regimens and restricted access to public health services for chronic conditions in times of lockdown and social distancing. Not to forget is the major impact on mental health of young people. On the other hand, young people are also critical in promoting preventive messages for risk mitigation, disseminating information to their families, peer groups and community, during this global crisis. Therefore, meaningful involvement of young people during the time of pandemic as well as prevention of NCDs is significant to the preparedness efforts for not only the current but also future public health crises.

### COVID-19 and Lung Health

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Currently evidence is lacking on how underlying lung disease will affect the severity and outcomes of COVID-19. The longer term impact of COVID-19 on lung health is unknown currently but with large numbers of people requiring high flow oxygen and/or ventilation there are concerns regarding residual lung damage in COVID-19 survivors. The data on these areas will be reviewed as well as discussing the what services need to be planned for COVID-19 survivors.

### Deadly partners – COVID-19 and Tobacco

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Tobacco smoking appears to be an important and entirely avoidable risk factor for a poorer prognosis in COVID-19. COVID-19 has not only severely constrained health systems but also could have a cascading impact on progress countries were making towards different goals and targets of the United Nations Sustainable Development Goals (SDGs). With the looming danger of economic recession, it becomes even more vital to avert the huge financial cost of tobacco use to the global economy. The urgency to prioritise stronger action on comprehensive tobacco control is mandatory for optimal response to contain the COVID-19 pandemic.

## Responding to COVID-19 and NCD risk factors

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Tobacco causes 8 million deaths every year and is a known risk factor for severe disease and death from many respiratory infections. Emerging evidence has suggested that smoking increases the risk of severe COVID-19 outcomes as well as the risk of death from COVID-19. However, in the absence of robust population studies to date, the association between smoking and infection with SARS CoV2 and between smoking and hospitalization has not been reliably quantified. This presentation will review the evidence on smoking and COVID-19 and will position the findings within the context of the wider literature and body of evidence. It will also look at risk communication of the findings on tobacco use and COVID in the overall context of harms from tobacco use that are well established.

## SP-14 Is TB elimination in the European Region a realistic goal?

### Mission Possible: TB elimination in Europe

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The European Union (EU) and European Economic Area (EEA) observes a decline in tuberculosis (TB) notification rate of about 5% per year. This is not enough to reach TB elimination or a reduction of the TB incidence rate of 80% by 2030 (SDG target).

The too slow decrease of TB incidence is partly due to the increasing percentage of TB cases in migrants; in many EU/EEA countries with a low TB notification rate, >75% of TB cases are among migrants. Cases in migrants need to be diagnosed and treated but may be hard to prevent if infection occurred outside of the EU/EEA. Therefore, elimination can be better defined as no local transmission as measured by whole genome sequencing. By using whole genome sequencing data (EU/EEA wide and from selected countries) the potential for TB elimination will be presented and challenges identified.

### **Mission Impossible: TB elimination in Europe**

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Projecting the incidence data of TB from the past decade into the future, suggests that elimination of TB in the European Union/European Economic Area (EU/EEA) might be achieved by 2035.

However, in a globalized world elimination of TB in the EU/EEA appears unlikely and even if this unlikely scenario would happen, the elimination of TB in Europe would still be far out of reach. Only a small fraction of patients with TB in Europe live in the EU/EEA. Some countries in central and Eastern Europe still have a high incidence of TB and Central/Eastern Europe is one of the hotspots of MDR/RR-TB globally.

The obstacles on the way to elimination are in all areas: prevention, diagnosis and treatment. Without a vaccine that protects contacts of patients with TB from the development of TB, elimination of TB will not be achieved, neither in Europe nor anywhere else.

### **Translational research and new tools in the pipeline to eliminate TB in low burden countries**

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TB elimination in low burden countries requires a comprehensive effort with existing and new tools. This presentation will familiarize the audience on recent diagnostic innovations in the pipeline to improve active case finding, infection detection and prediction of risk.

### **Access to care for vulnerable populations in Europe**

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Tuberculosis burden in Europe is particularly high among vulnerable population groups. These groups also have an increased risk of inadequate access to diagnosis and treatment results. This is why access to health care for vulnerable groups, including migrants, is both important for individual care of patients and to ensure a reduction of transmission that would be necessary for TB elimination in Europe.

Here, we will discuss:

- 1) current evidence on access of care for vulnerable population groups in Europe;
- 2) evidence on strategies and policies effective at increasing access to care and lowering transmission of tuberculosis, and,
- 3) some considerations on ethics, equity and legal issues in the design of these policies.

### **Research collaborations informing TB control strategies in Europe: TBnet and ERS-CRC approach**

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TBnet has performed a large number of clinical and operational studies in the field of TB. The consortium is supported by the European Respiratory Society, through a Clinical Research Collaboration. The activities provided insight in - amongst others - the unequal distributions across Europe in terms of: infection control facilities; the staff available, and inpatient vs. outpatient management of TB; the inclusion of "hard to reach" groups; the cost and availability of molecular diagnostic tests for MDR-TB; the availability, cost and stability of drug supply; adverse effects of new drugs; and the confounding effect of relapse on treatment outcomes.

## **SYMPOSIA: THURSDAY 22 OCTOBER 2020**

### **SP-15 Short, all-oral regimens for rifampicin-resistant TB: progress towards programmatic implementation at country level.**

#### **Early adoption of a modified, all-oral shorter RR-TB regimen with Group A and Group B drugs in Georgia**

N Lomtadze,<sup>1</sup> <sup>1</sup>National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia. e-mail: nlomtadze@gmail.com

Given high prevalence of intolerance/confirmed resistance to several drugs in the standardized, injectable-based shorter regimen, Georgia initiated guideline revisions and protocol development after WHO Consolidated Guidelines in December 2018.

In addition to guidance for longer all-oral RR-TB regimens, national guidelines recommend a modified, all-oral shorter regimen (mSTR) of bedaquiline/linezolid/levofloxacin/clofazimine/cycloserine for 9 months, with delamanid substitution for toxicities. The guidelines and protocol were submitted to the Ministry of Health in January 2019, approved in June 2019, and fully implemented the same month. To ensure rapid transition, drug quantification and ordering, and training for all clinicians and staff, took place in parallel to approval processes.

While national policy allows use of mSTR programmatic, Georgia is committed to evidence generation as part of WHO Euro's operational research initiative. As of April 2020, 106 patients have received mSTR; 17 have completed treatment with cure, 2 lost to follow-up, and 87 remain on treatment.

#### **Rapid implementation of an all-oral shorter RR-TB regimen during the COVID-19 pandemic in the Philippines**

M Santiago,<sup>1</sup> <sup>1</sup>Family Health International 360, Makati, Philippines. e-mail: maryrosarytaguinod0@gmail.com

To improve on successful treatment outcomes of 58% in patients with RR-TB in 2016, the Philippines introduced the standardized, injectable-based shorter regimen (SSTR) in January 2017 under program conditions. Treatment success of 68% for patients receiving the SSTR in 2017 revealed high rates of lost to follow up primarily due to adverse events from the injectable agent. The National TB Control Program met in Janu-

ary 2020 to plan the transition to an all-oral shorter regimen based on WHO's December 2019 Rapid Communication; a departmental memorandum in February 2020 mandated all health facilities providing DR-TB services to implement a standardized, shorter, all-oral bedaquiline based RR-TB regimen (SSOR) by 1 March 2020.

Additional orientation and trainings on the guideline update were provided in March-April 2020; despite the evolving COVID-19 pandemic, within one month from release of local guidelines there are more than 150 patients enrolled on SSOR in the Philippines.

#### **Adopting best practices in RR-TB management in Zambia: implementation of WHO recommendations for all-oral RR-TB regimens**

P Lungu,<sup>1</sup> <sup>1</sup>National Tuberculosis Programme, Lusaka, Zambia. e-mail: lungupatrick99@gmail.com

Of the 507 patients started on treatment in Zambia in 2018, 357 (70%) started on the 2016 WHO recommended standardized shorter regimen, 132 (26%) started on a longer, conventional regimen, and 18 (4%) started on an individualized regimen with bedaquiline. By the end of second quarter 2019, 60% of all patients started on RR-TB treatment were receiving a fully oral, bedaquiline-based longer regimen. The National TB Programme of Zambia has kept pace with WHO recommendations, most recently with an addendum to the national RR-TB guidelines, finalized in September 2019, with immediate plans to phase out the injectable based shorter regimen and move to fully-oral regimens for a majority of newly diagnosed RR-TB patients. By the start of 2020, all RR-TB patients are being commenced on injectable-free regimens.

This presentation will describe the subsequent transition from injectable agents to bedaquiline within the shorter regimen from the perspective of clinicians and patients.

#### **Impact of the COVID-19 pandemic on full implementation of all-oral shorter RR-TB regimens in Pakistan**

A Ghafoor,<sup>1</sup> <sup>1</sup>National TB Programme, Islamabad, Pakistan. e-mail: ghafoora177@gmail.com

The National TB Program (NTP) is among the lead countries with prompt implementation of World Health Organization RR/MDR-TB recommendations and guidelines whenever required. The all-oral longer treatment regimen containing bedaquiline was initiated in July 2019, with over 900 patients having received bedaquiline by December 2019.

Following issuance of WHO Rapid Communication on the use of an all-oral shorter treatment regimen in the same month, the NTP subsequently circulated an advi-

sory in January 2020 to start enrolling eligible patients on a shorter regimen containing bedaquiline instead of amikacin. The advisory was immediately put into implementation at all 33 PMDT sites across the country. However, due to the emergence of the current COVID-19 pandemic in Pakistan, enrolments on the all-oral shorter regimen have not met full potential and the pandemic response is seen as a huge challenge in optimum implementation.

### **SP-16 Health system response preventing TB and tobacco - lessons learned from COVID-19**

#### **The Union approach in establishing tobacco control into health system**

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Tobacco smoking appears to be an important and entirely avoidable risk factor for a poorer prognosis in COVID-19. COVID-19 has not only severely constrained health systems. With the looming danger of economic recession, it becomes even more vital to avert the huge financial cost of tobacco use to the global economy. The urgency to prioritise stronger action on integration of TB and tobacco control measures are mandatory. The Union approach ABC (ask, brief advice, cessation support) can be universally applied as it has produced more than 60% smoking quit rates among people with TB in India, Indonesia, China, Bangladesh and Philippines. Time to scale-up.

#### **How effective is the systemic integration of smoking cessation into tuberculosis control programme in creating smoke-free environments in Manila?**

A Ohkado,<sup>1</sup> <sup>1</sup>Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Kiyose, Japan.  
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We conducted a prospective observational study, whereby an intervention group comprised of TB patients receiving the modified ABC Smoking Cessation approach, and a control group receiving only regular health education, at selected health centers in Manila City.

We enrolled in 1,144 and 1,030 TB patients as an intervention and a control group, respectively. Tobacco smoking rates at registration indicated no significant difference between the groups, 31.6% vs. 27.3%, respectively. Both tobacco smoking and second-hand smoking rates throughout the TB treatment period were lower in

the intervention group than in the control group. In contrast, there was no significant difference in TB treatment success rate between these groups, 85.0% vs. 87.3% ( $P=0.201$ ), respectively, and the self-claimed health status at month 12 ( $P=0.132$ ).

#### **COVID-19: a window of opportunity to prompt tobacco cessation**

M Llambi,<sup>1</sup> <sup>1</sup>University of the Republic, Montevideo, Uruguay. e-mail: llambil@hc.edu.uy

An initiative from academia, professional associations, and civil society from several Latin American countries and Spain regarding COVID-19 and tobacco use will be presented. We prepared an evidence-based Position Statement focused on two questions:

Do smokers have higher risk of acquiring SARS-COV-2 infection and developing COVID-19? And, do they have a more acute progression or a worse prognosis?

The document was disseminated through webs, social media and traditional media, placing tobacco cessation in the COVID-19 agenda.

As a result of this initiative, further steps regarding tobacco cessation and tobacco surveillance in the COVID-19 contingency were achieved.

#### **Tobacco cessation among people with TB in Dhaka, Bangladesh**

M Islam,<sup>1</sup> <sup>1</sup>BRAC, Dhaka, Bangladesh.  
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An intervention of tobacco cessation in people with TB was made with the support of NTP in Dhaka city. Front-line health workers identified tobacco users and level of addiction to tobacco through interview.

Every patient with history of tobacco use was registered for counselling for tobacco cessation. Brief advice was given at registration and follow-up visits (2/3, 5, 6 months). In 2018 and 2019, a total of 13,579 patients were registered in BRAC support TB centres. Of them, 3012 patients were tobacco users (86% male, 14% female). Of the total tobacco users, 938 (31%) have high level of tobacco addiction and 2074 (69%) have low level of tobacco addiction.

At the end of treatment, a total of 1716 (57%) TB patients quitted tobacco use. This simple intervention could help to quite tobacco use over 505 of the TB patients at the end of treatment.

## SP-17 Detecting TB among people living with HIV: updated options with updated guidance

### The TB/HIV Testing Landscape: WHO Policy Updates

A Korobitsyn,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: korobitsyna@who.int

In 2018, an estimated 0.86 million (8.6%) of the 10.0 million people who developed TB worldwide were HIV-positive. Traditional diagnostic methods often are less sensitive in HIV-positive TB patients, as these patients often have paucibacillary forms of TB. Unlike traditional diagnostic methods, urinary LAM assays demonstrate improved sensitivity for the diagnosis of TB among this group of patients. In May 2019 WHO has convened Guideline Development Group (GDG) meeting, where the evidence on use of commercially available urinary LAM test were evaluated.

The outcome was extending WHO recommendations on use of the test to broader group of people living with HIV (PLHIV). Conventional NAAT tests are recommended for PLHIV as well. In December 2019 WHO has convened GDG meeting, where the evidence on use of several NAATs were evaluated and recommendations updated. Xpert MTB/RIF, Xpert Ultra, Truenat MTB, MTB Plus, MTB-RIF Dx were recommended for broader patients groups, including PLHIV.

### How? Practical Global Laboratory Initiative Resources to Support Updated WHO TB/HIV Testing Guidance

H Alexander,<sup>1</sup> <sup>1</sup>US CDC, Atlanta, United States. e-mail: drz5@cdc.gov

On behalf of the Stop TB Partnership's Global Laboratory Initiative (GLI), Dr. Heather Alexander will review GLI resources to support countries to review, implement and ensure quality for TB/HIV diagnostic testing strategies, policies, algorithms and networks.

Highlights will include presentation of the GLI TB Diagnostics Implementation Manual, the revised TB Model Algorithm for persons living with HIV and the Practical Guide for TB LAM Implementation. Polling will be used throughout the presentation to review anonymous audience familiarity with up-to-date TB/HIV testing concepts and resources, and provide real-time feedback to GLI on themes of interest for further support.

Participant responses may be used to guide live GLI website review of materials and resources for audience familiarity and quick reference.

## Xpert MTB/RIF Ultra and LF-LAM: Lessons Learned from South Africa

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South Africa is an early adopter of new TB tools. Two such diagnostics implemented are the Xpert MTB/RIF Ultra and the LF-LAM. Whilst the improved sensitivity of the Xpert MTB/RIF Ultra allows detection of more cases, a challenge emerged in managing a 'trace' result especially in light of the high proportion of previously treated TB in the country. Using the preliminary findings of the National TB prevalence survey, an algorithm addressing the management of Xpert Ultra 'trace' results was developed and will be shared.

The LF-LAM testing algorithm for PLHIV was developed in 2018 through the National TB Think taking into account clinical considerations. Training was initiated nationwide, for a roll out as a point of care diagnostic, and introduced in a phased approach. Several challenges have hampered implementation: kit availability, recording of results, competency in performing the test, task shifting etc. A hybrid model is now considered.

## Molbio Diagnostics Truenat™ MTB, MTB Plus and MTB-RIF: Lessons Learned from India

S Sarin,<sup>1</sup> <sup>1</sup>Foundation for Innovative New Diagnostics (FIND), Delhi, India. e-mail: Sanjay.Sarin@finddx.org

Molbio Diagnostics (India) has developed chip-based RT-PCR assays for detection of TB i.e. Truenat™ MTB and the MTB-RIF Dx reflex assay for detection of RIF resistance. Basis interim data from a FIND-coordinated multi-centric, prospective field evaluation study, the performance of Truenat MTB, MTB Plus and MTB-RIF Dx assays showed comparable accuracy with Xpert MTB/RIF and Xpert MTB/RIF Ultra for TB detection and for sequential rifampicin resistance detection (WHO 2020).

Truenat has been approved for use by India's National TB Elimination Program (NTEP) as a potential replacement for the smear microscopy test. There are currently 300+ Truenat platforms in India with a majority of them in the southern state of Andhra Pradesh. The Government of India is in the process of adding another ~1500 Truenat machines within the NTEP.

The presentation will focus on the initial learnings from implementation that can be leveraged for a successful national, and potentially international scaleup.

### **Challenges with maintaining quality of TB Xpert results in a low-resource country**

M Joloba,<sup>1</sup> <sup>1</sup>Supranational TB Reference Laboratory, Ministry of Health, Kampala, Uganda.  
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As TB diagnostic networks expand in test scope, across far-reaching geography and across tiers of the laboratory network, additional resources are needed to ensure that accurate, reliable and timely test results are produced. Since 2011, the TB Xpert diagnostic network has expanded significantly in Uganda to include 250 testing sites that have evolved from use of the Xpert MTB/RIF assay to the more sensitive, Xpert MTB/RIF Ultra. Quality assurance efforts have had to similarly expand to support training at the site- and above-site levels, production and use of quality management system documentation, conductance of internal and external quality assurance activities and that all efforts are matched with appropriate monitoring, evaluation and corrective action, as needed. In a resource-limited setting, these dual expansions challenge the health system and program and require innovative approaches for support.

### **SP-18 The work of the WHO European Laboratory Initiative on TB, HIV and viral hepatitis**

#### **European Laboratory Initiative (ELI) on TB, HIV and viral Hepatitis: supporting countries of the WHO European Region on integrated laboratory capacity building strategies**

S EHSANI,<sup>1</sup> <sup>1</sup>World Health Organisation, Copenhagen, Denmark. e-mail: ehsanis@who.int

The WHO European Region established the European Laboratory Initiative in 2012, in collaboration with the Global Laboratory Initiative, to strengthen laboratory capacities for accurate diagnosis and early detection of TB and drug resistant TB in the WHO European Region.

In 2018, ELI's mission was expanded to upscale the detection of TB/HIV coinfection, HIV and viral hepatitis, with the ultimate objective of strengthening and making more efficient use of existing capacities for all 3 diseases. During the COVID-19 pandemic this integrative capacity building approach has proven to be beneficial not only for TB, HIV and viral Hepatitis but also for SARS-CoV-2 testing. This presentation gives an overview of the ELI's activities.

### **Algorithm for laboratory diagnosis and treatment-monitoring of pulmonary tuberculosis and drug-resistant tuberculosis using state-of-the-art rapid molecular diagnostic technologies**

F Drobniewski,<sup>1</sup> <sup>1</sup>Imperial College London, London, United Kingdom. e-mail: f.drobniewski@imperial.ac.uk

The WHO European Laboratory Initiative has produced a key technical document describing how TB laboratories and programmes in the WHO European Region can increase the timely and accurate detection of TB and MDR TB.

The approach emphasises the importance of molecular based diagnostics through the use of detailed algorithms for diagnostic and treatment progression. It helps laboratories and clinicians improve their joint understanding of what the test results mean, their limitations, and the therapeutic actions that follow. It builds on the ELI online courses which provide practical training on the interpretation of WHO endorsed tests for drug resistant TB.

### **ELI online course on Drug-resistant tuberculosis: how to interpret rapid molecular test results**

C Koeser,<sup>1</sup> <sup>1</sup>University of Cambridge, Cambridge, United Kingdom. e-mail: cuk21@cam.ac.uk

The European Laboratory Initiative for TB, HIV and Viral Hepatitis has recently launched a free online course that provides practical guidance and expert advice on the interpretation of selected WHO-endorsed tests for drug-resistant TB. More specifically, it covers the latest guidance for the interpretation of rapid molecular drug-susceptibility testing assays by Cepheid (GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra) and Hain Lifescience (GenoTypeMTBDRplus VER 2.0 and GenoTypeMTBDRsl VER 2.0).

This presentation will introduce the course, assess its reception to date and outline future plans.

### **Integration of multi-disease testing platforms for infectious diseases to maximise the benefit in time of need: using TB, HIV, and hepatitis C as an example.**

D Simoes,<sup>1</sup> <sup>1</sup>Institute of Public Health - University of Porto, Porto, Portugal. e-mail: daniel.simoes@gatportugal.org

The presentation will focus on the role that integrated diagnosis and monitoring responses can have in the region as a means to provide high quality, more person centred services, making use of the systems already in place.

Drawing on examples from TB, HIV and Hepatitis C, it will reflect on opportunities and barriers moving forward, and provide examples of how systems can adjust in order to provide more effective responses.

### **External Quality Assurance Dashboard for TB Drug Susceptibility Testing: why a once a year evaluation is insufficient to guarantee for quality DST results**

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The use of WHO recommended new anti-TB medications is emphasized in the new guidelines. High quality drug susceptibility testing (DST) and high DST coverage for notified TB cases is required. There is a global challenge with the number of bacteriologically confirmed notified TB cases, despite excellent annual panel testing results.

To ensure the quality of phenotypic DST, and verify the steps of diagnostic process, a comprehensive DST Assessment Tool has been developed to be used independently by laboratory workers. The tool is aimed to identify gaps and suggest ways to improve the drug susceptibility testing:

- i) evaluation the performance and role of the laboratory in bacteriological confirmation among notified TB cases;
- ii) quick identification of weak points in the existing laboratory workflow;
- iii) recommendations for laboratory development;
- iv) standardization of assessment process, uniform results;
- v) help in implementation of the recommended algorithm and laboratory quality indicators calculation.

### **SP-19 Household and close contact investigation: a key gateway to TB prevention and case detection in children**

#### **Assessing the risk of tuberculosis in children after close exposure: implications for implementation of contact investigation interventions in high TB burden countries**

L Martinez,<sup>1</sup> <sup>1</sup>Stanford University, Palo Alto, United States. e-mail: leomarti@stanford.edu

Globally, tens of millions of children are exposed to an individual with TB annually. Drawing upon a multi-cohort collaboration of research groups, we aimed to explore two questions:

- (i) estimating the risk of developing tuberculosis by time-period of follow-up, demographics (age, region), and clinical attributes (HIV, tuberculosis infection status, previous tuberculosis); and,
- (ii) estimating the effectiveness of preventive therapy and BCG vaccination on the risk of developing tuberculosis.

The results of this work will be presented in this session showing that the risk of developing tuberculosis among exposed infants and young children is very high and that most cases occurred within weeks of contact investigation initiation and might not be preventable through prophylaxis.

Taken together, these findings suggest that alternative strategies for prevention are needed, such as earlier initiation of preventive therapy through rapid diagnosis of adult cases or community-wide screening approaches.

#### **Implementation of contact investigation and TPT provision in Nepal**

S Shrestha,<sup>1</sup> <sup>1</sup>Save the Children, Kathmandu, Nepal.  
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Before 2017, the Nepal NTP mainly focused on passive case finding with limited ACF activities. Contact tracing was implemented by the NTP in 38 of high TB burden districts since early 2017. All household contacts undergo symptom screening and those screening positive are referred for TB evaluation, while children <5 without symptoms are referred for TPT. Contact tracing of 27,982 bacteriologically confirmed TB cases was done between March 2018 and December 2019. 3,735 children were initiated in TPT, with 96.8% retained in treatment (completing or still on treatment) and 3.2% discontinuing. Results have shown that contact tracing and a strong care cascade for TPT can be achieved in a low-resource setting, with apparent an immediate impact on TB outcomes. Programme will be scaled-up throughout Nepal, through provision of adequate budget from both government and donors maintaining routine supervision to ensure adherence and completion of TPT.

### **Implementing household contact investigation in high TB burden, resource-limited settings: lessons learnt from a multi-country project in 9 sub-Saharan countries**

M Casenghi,<sup>1</sup> <sup>1</sup>Elizabeth Glaser Pediatric AIDS Foundation, Geneva, Switzerland. e-mail: mcasenghi@pedaids.org

Contact Investigation is recognized as an important intervention and it serves as a key entry point for both pediatric TB case finding and prevention. However, roll-out and scale-up of contact investigation interventions remain challenging in high TB burden countries. The CaP TB project has implemented contact investigation interventions across 9 sub-Saharan African countries and evaluated the cascade of care for both TB detection and TB preventive treatment (TPT).

This presentation will review the evidence generated so far by the project, including early experiences on the use of the 3RH regimen under routine conditions, and discuss practical lessons learnt on strategies and approaches that can improve implementation of contact investigation.

### **Moving to shorter regimens for TB preventive Treatment in children: current and future opportunities**

N Salazar-Austin,<sup>1</sup> <sup>1</sup>Johns Hopkins School of Medicine, Baltimore, United States. e-mail: nsalaza1@jhmi.edu

Tuberculosis is a top cause of pediatric TB morbidity and mortality. Identifying recently exposed children and initiating TB preventive treatment (TPT) has been long-standing approach to TB control. Short-course TPT has recently been endorsed by the WHO and is an attractive solution to improving uptake and completion rates. There are many considerations for countries as they roll out short-course TPT for household child contacts and CALHIV.

We will describe the current landscape for short-course TPT in both of these populations and highlight the gaps in our knowledge as they relate to pediatric dosing, drug interactions and efficacy. We will conclude with timelines for pediatric formulations for rifapentine and current research into 1HP and other novel short-course regimens.

### **SP-20 Improving access to laboratory-based diagnosis for young children - recent advances using stool and urine as alternative sample types.**

#### **Closing the case detection gap in children with TB: WHO updates**

S Verkuijl,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: verkuijls@who.int

Over 1.1 million children (aged under 15 years) were estimated to have fallen ill with TB in 2018 and over 200,000 of them died, the majority before their 5th birthday. The case detection gap was estimated at 54% and was highest (63%) in children under five, due to among others the paucibacillary nature of TB, the lack of a sensitive point-of-care test and the challenges in collecting a respiratory sample for bacteriological testing in young children.

This presentation will set the scene covering the latest epidemiological data on TB children as well as progress towards the United Nations High Level Meeting on TB targets for children. Updated WHO policy recommendations relevant to the diagnosis and management of TB in children will be discussed.

#### **Utility of stool samples for microbiological confirmation of TB in children**

P Nabeta,<sup>1</sup> <sup>1</sup>FIND, Geneva, Switzerland. e-mail: Pamela.Nabeta@finddx.org

In January 2020 the WHO published a Rapid Communication on the use of molecular assays as initial tests for the diagnosis of TB. The conclusions support the continued use of Xpert MTB/RIF and Xpert Ultra in children including stool samples.

Following up on last year's symposium, two parallel evaluations of centrifuge-free stool processing methods are underway, including the Stool Processing Kit (FIND), Simple One-Step (KNCV) and Sucrose Flotation (TB-Speed) methods, in combination with Xpert Ultra.

The head-to-head comparison includes an assessment of the performance for TB detection as well as the ease of use of the three methods.



### **Update Simple One step stool testing method and practical guidance on the best placement of this test in the diagnostic algorithm**

E Tiemersma,<sup>1</sup> <sup>1</sup>KNCV, The Hague, Netherlands.  
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To assess the accuracy, feasibility and acceptability of the KNCV SOS stool method as compared to Xpert on a gastric aspirate or an induced sputum specimen, the SOS stool method is being implemented in parallel to the routine algorithm in Ethiopia and Indonesia. This will provide more precise accuracy estimates and valuable lessons for scale up. Modeling studies are underway to provide more insights into the best placement of the method in the diagnostic algorithms.

This presentation will outline key lessons learned needed to be addressed for scale up of stool processing in countries and provide insights on how it can best be placed in the diagnostic algorithm for childhood TB.

### **Accuracy of a novel urine test, Fujifilm SILVAMP TB LAM, for the diagnosis of pulmonary tuberculosis in children**

M Nicol,<sup>1</sup> <sup>1</sup>University of Western Australia, Perth, Australia.  
e-mail: mark.nicol@uwa.edu.au

An accurate point-of-care test for tuberculosis in children remains an elusive goal. A novel urinary lipoarabinomannan (LAM) test, Fujifilm SILVAMP TB LAM (FujiLAM) showed superior sensitivity to Alere Determine TB LAM (AlereLAM) in HIV-infected adults.

We compared the accuracy of FujiLAM and AlereLAM in children with suspected pulmonary tuberculosis presenting to hospital in Cape Town, South Africa. 204 children were enrolled and had valid results from index and sputum tests. Using a microbiological reference standard, sensitivities of FujiLAM and AlereLAM were similar (42% and 50% respectively), but lower than Xpert MTB/RIF of sputum (74%).

However specificity of FujiLAM was substantially higher than AlereLAM (92% vs. 66%), suggesting that non-specific detection accounted for the apparent higher sensitivity of AlereLAM. Sensitivity of FujiLAM was higher in HIV-infected and malnourished children.

The high specificity of FujiLAM suggests utility as a 'rule-in' test for tuberculosis in children, particularly those who are HIV-infected.

### **SP-21 Engaging communities to address concurrent pandemics of TB and COVID-19**

#### **Field notes: a frontline CHW perspective on responding to TB in the time of COVID**

P Muedi,<sup>1</sup> <sup>1</sup>TB Proof, Pretoria, South Africa.  
e-mail: mp.muedi@gmail.com

CHWs play a critical role in supporting person-centred care: raising TB awareness, providing TB information in local languages to communities and reaching missing people with TB who are not accessing health services and linking them to the health system. Each person has a human right to health and CHWs play a critical role in transforming the TB response to be equitable, rights-based and people-centred. Yet, CHWs are not provided with platforms to inform the TB response despite being experts on the healthcare needs of communities.

Ms. Muedi will discuss insights from frontline CHWs, including identified gaps in the training and personal protective equipment offered to CHWs caring for people with TB and the role of CHWs in the response to COVID-19.

#### **Prioritizing partnerships – mobilizing CHWs to fight COVID-19 in Peru**

L Lecca,<sup>1</sup> <sup>1</sup>Socios En Salud, Lima, Peru.  
e-mail: llecca\_ses@pih.org

Socios En Salud (SES) has partnered with the United States Agency for International Development to support Peru's healthcare system to care for patients with COVID-19. Dr. Lecca will discuss how SES activated a community health worker network to safely conduct outreach visits to identify families needing clinical and social support in Peru's hardest-hit regions of Lima, and a medical call center to tele-health consultations. Dr. Lecca will discuss how SES applied its many years of experience mobilizing CHWs to contact public health education and contact tracing for TB in order to train CHWs to safely provide community-based care and education.

#### **Bending the curve: Leveraging experiences from TB care to contain COVID-19 in Massachusetts**

K Seung,<sup>1</sup> <sup>1</sup>Partners In Health, Boston, United States.  
e-mail: kjseung@pih.org

Partners In Health is a non-governmental organization that has built long standing relationships with ministries of health and communities in the world's poorest settings, with the goal of providing the highest standard of

care to all. As such, they are well-positioned to tackle COVID-19, which is having a disproportionate impact on communities already affected by poverty and poor healthcare. Dr. Seung will discuss how PIH developed an ambitious response that sought to bend rather than merely flatten the curve of COVID-19 in Massachusetts and other U.S. states by applying lessons learned from TB with respect to testing, contact tracing, and supported quarantine and isolation. He will discuss the challenges of implementing rapid testing and addressing the social and economic needs of underserved communities, including the use of food and cash assistance, as part of a comprehensive response.

### **Engaging policymakers to protect Community Health Workers**

I Schoeman,<sup>1</sup> <sup>1</sup>TB Proof, Pretoria, South Africa.  
e-mail: ingrid.tbproof@gmail.com

Ms. Schoeman will discuss insights gained from leading a Gates Foundation funded project to empower CHWs to motivate for and contribute to person-centred TB care, by providing training in advocacy, media and communications.

In response to stigma being identified as a major barrier in the TB care cascade, she helped to facilitate CHWs in Hammanskraal, Gauteng province, to develop community-focused theatre plays to address stigma. She will discuss the challenges of building and maintaining strong relationships locally, provincially and nationally in order to secure support for in-service TB training of CHWs and for an implementation plan to accompany the Ward Based Primary Health Care Outreach Team policy that was recently released by the Department of Health.

Finally, she will examine how TB Proof was able to leverage its TB advocacy partnerships to advocate to the South African government to impose a lockdown and #Masks4All policy to disrupt COVID-19 transmission.

### **SP-22 Advancing a prevention research agenda for TB**

#### **Prevention through Vaccination: Advancing research and development of new vaccines to prevent TB**

G Kaguthi,<sup>1</sup> <sup>1</sup>Kenya Medical Research Institute, Nairobi, Kenya. e-mail: skiringa@gmail.com

Vaccines are one of the most successful and effective public health interventions to decrease the spread of life-threatening infectious diseases. Worldwide, incidence and death due to measles, diphtheria, influenza, polio, meningitis and numerous other diseases have been greatly reduced through effective vaccines and immunization programs.

However, BCG, the only licensed vaccine to prevent TB, has been inadequate in halting the global epidemic. Over the past two decades there has been a significant global effort to develop new, more effective TB vaccines, and recent promising results have demonstrated that developing new vaccines is feasible, bringing increased enthusiasm and optimism to the field.

This presentation will discuss the latest advances in the research and development of new, more effective vaccines to prevent TB, the potential impact a new TB vaccine could have on TB incidence, and what will be necessary to further advance the TB vaccine pipeline.

#### **Diagnosing TB Infection (TBI) to prevent TB: an overview of the landscape of TBI and incipient TB tests**

M Ruhwald,<sup>1</sup> <sup>1</sup>Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland.  
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Existing tests for TBI, tuberculin skin test (TST) and Interferon Gamma Release Assays (IGRA), have limited value in predicting risk for the progression from infection to active TB. Furthermore, implementation of TBI tests faces operational challenges such as cold chain requirements and needs for sophisticated laboratory infrastructure.

Partly as a result of logistic challenges and limitations in their accuracy, TBI tests are not required prior to start of TB preventive treatment (TPT) in priority risk groups: PLHIV and household contacts aged less than 5 years. For others, TBI tests are generally recommended to identify those who benefit most from treatment. New tests for TBI are emerging such as the C-Tb (Serum Institute of India), Diaskin Test (Generium, Russian Federation) and QFT access (Qiagen, SA).

It is important to review the landscape of TBI tests and identify gaps that need to be filled to facilitate development and introduction of new tests.

### **TB Preventive Therapy: Treatment of Latent TB Infection with a Shorter Course Regimen**

R Chaisson,<sup>1</sup> Johns Hopkins Center for Tuberculosis Research, Baltimore, United States.  
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Roughly one quarter of the world is infected with latent Tuberculosis infection (LTBI) and treating this population is critical to achieving the ending the Tuberculosis epidemic. While treatment of active Tuberculosis has remained a top priority, this strategy alone will not yield the needed results to meet these END TB targets. Current treatments for LTBI can take up to 9 months and adherence to such lengthy treatments have proved inconsistent in the past. Newer, shorter-course preventative therapies are needed if we are to achieve the reductions in TB cases needed to meet the END TB targets.

### **What's law got to do with it? New technologies for TB prevention and emerging human rights issues**

B Citro,<sup>1</sup> Northwestern Pritzker School of Law, Chicago, United States. e-mail: citro@law.northwestern.edu

The role of law and human rights in the global TB response have been increasingly recognized as central to achieving global targets set in the End TB Strategy and the UN Political Declaration on TB.

Despite this, there is a lack of understanding and implementation of a human rights-based disease response. As new vaccine, diagnostic and treatment technologies emerge, including to prevent TB infection and/or disease and to diagnosis and treat latent TB infection, the law and rights will play an even greater role in either supporting or hindering efforts to end the epidemic.

Building on the other talks in this session, this presentation will consider the opportunities and risks associated with legal frameworks and human rights law to promote the availability and accessibility of new TB preventive technologies. The talk will focus on intellectual property and trade law and the rights to health and science.

### **SP-23 Preventing TB in people with diabetes mellitus: where are we now and where are we going?**

#### **Risk of tuberculosis infection in health care workers in relation to blood glucose levels and vitamin D status**

G Davaasambuu,<sup>1</sup> Harvard Medical School and Department of Nutrition at Harvard T. H., Boston, United States. e-mail: gdavaasa@hsph.harvard.edu

The association between DM and TB has been known for many years but studies in the last 15 years highlighted that DM increases the risk of TB and that patients with dual disease have worse TB treatment outcomes compared with those who have just TB alone.

This was a cross-sectional study sought to understand whether the association between vitamin D and TB risk is modified by fasting blood glucose (FBG) among adult health care professionals working in TB hospitals of Mongolia. Adult healthcare workers (doctors, nurses, laboratory staffs, etc) who work in the chosen sites will be recruited and assessed for TB infection using the QuantiFERON-TB Gold Plus (QFT-Plus) assay.

Participants will undergo assessment of serum 25-hydroxyvitamin D (25(OH)D), FBG, and lifestyle characteristics.

#### **Rifampentine-based short-course preventive therapy for DM patients with LTBI**

J Wang,<sup>1</sup> National Taiwan University College of Medicine, Taipei, Taiwan. e-mail: jywang@ntu.edu.tw

Began from 2018, a pilot project for screening and treating LTBI in TB high-risk populations was launched by Taiwan CDC. In Taichung and Kaohsiung cities, persons with poorly-controlled DM, defined as HbA1c = 9% within recent one year, were chosen as the target population for intervention. Between April 2018 and August 2019, a total of 833 subjects were screened by DM specialists and 779 (93.5%) received LTBI testing by QuantiFERON, with a positive result in 200 (25.7%).

After being evaluated by pulmonologists, 2 had active pulmonary TB and 49 declined preventive therapy. In the remaining 149 (female: 63), mean age was 65.2±8.9 and BMI 26.5±3.8. Of them, 45 and 104 received 9H and 3HP regimen, with 38 (84%) and 88 (85%) completing treatment, respectively. In the 3HP group, 7 (7%) suffered from systemic drug reactions.

This pilot project demonstrates LTBI policy can be efficiently implemented under collaborative framework.

### **Progression from LTBI to active TB disease and effectiveness of Isoniazid chemoprophylaxis in persons Living with diabetes: an individual-participant Meta-Analysis**

L Martinez,<sup>1</sup> <sup>1</sup>Stanford University, Palo Alto, United States. e-mail: leomarti@stanford.edu

Globally, hundreds of millions of people are living with diabetes (PLWD) and are at increased risk of developing tuberculosis. Drawing upon a multi-cohort collaboration of research groups, we aimed to explore two questions:

- (i) is the increased risk of tuberculosis among PLWD predominantly due to increased risk of infection or disease progression? and
- (ii) how effective is isoniazid in the prevention of tuberculosis among PLWD with Mycobacterium tuberculosis infection?

The results of this work will be presented in this session showing that the increased risk of developing tuberculosis is due to an elevated risk of progression from M. tuberculosis infection to disease and that isoniazid preventive therapy is highly effective in preventing tuberculosis among PLWD. Taken together, these findings suggest that PLWD should be prioritized for preventive therapy.

### **Prevention of tuberculosis in diabetes (PROTID); a phase 3 randomized trial**

R Crevel,<sup>1</sup> <sup>1</sup>Radboud university medical center, Nijmegen, Netherlands. e-mail: Reinout.vanCrevel@radboudumc.nl

PROTID ([www.protid-africa.com](http://www.protid-africa.com)) is the first RCT globally to examine TB preventive treatment among people with DM (n=3000), comparing 3HP preventive therapy and placebo, with incident TB disease over 2 years as the primary endpoint. In parallel with the RCT, a cohort of 1000 people with DM, but without evidence of LTBI will be followed to confirm whether TB incidence in this group is indeed too low to warrant preventive treatment.

PROTID will also evaluate optimal ways to screen people with DM for LTBI and TB; address gaps in prevention and therapeutic management of combined TB and DM; and estimate the population impact and cost-effectiveness of LTBI treatment in people living with DM on TB incidence and transmission.

### **SP-24 The impact of COVID-19 on TB research and development and access: it's a two-way street**

#### **COVID-19 and TB research**

F Cobelens,<sup>1</sup> <sup>1</sup>University of Amsterdam, Amsterdam, Netherlands. e-mail: f.cobelens@aighd.org

TB research initiatives have largely been put on pause, throwing off trial timelines and delaying long-anticipated results necessary for rolling out new tools to optimize the prevention, diagnosis, and treatment of TB. Yet, TB research investments, innovations, and infrastructure are being leveraged to help advance research and development initiatives focused on addressing the global COVID-19 pandemic.

This talk will explore both how TB research is being impacted by and benefitting COVID-19 related research.

#### **COVID-19 and access to TB tools**

M Pai,<sup>1</sup> <sup>1</sup>McGill University, Montreal, Canada. e-mail: madhukar.pai@mcgill.ca

TB program investments, interventions, and infrastructure are supporting government efforts to mitigate the spread and severe effects of COVID-19. The need to scale up the response to COVID-19 in high TB burden countries is urgent and necessary to save lives. Still, TB program activities and services must continue and expand, both to prevent unnecessary morbidity and mortality and to keep us on track for ending TB.

This talk will discuss the synergies between the global response to COVID-19 and TB, and how to ensure that TB tools which may be able to assist in the COVID-19 response are used in a way that does not reduce access to them by TB programs.

#### **COVID-19 and access to TB innovations**

S Madoori,<sup>1</sup> <sup>1</sup>Treatment Action Group, New York, United States. e-mail: suraj.madoori@treatmentactiongroup.org

The urgency of the COVID-19 pandemic has mobilized unprecedented political will and consensus regarding ideas long promoted by the global access to medicines and innovations movement.

This talk will cover access principles and proposals that have gained traction, and how they may have lasting benefits and applications for activists working to promote access to TB innovations and the benefits of TB research and scientific progress.

### **COVID-19 in a parallel universe, with adequate funding for TB R&D**

G Brigden,<sup>1</sup> The Union, Geneva, Switzerland.  
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Investments in global health, and TB in particular, have translated to many benefits to the global response to COVID-19. But imagine a world in which research and the global response to TB hadn't been underfunded for the last 50 years. What scientific gains would have been possible, and how could these gains have given us an advantage in our ability to control the COVID-19 pandemic and prevent unnecessary deaths and suffering?

### **SP-25 It takes more than bandwidth - using the Extension for Community Healthcare Outcomes virtual community of practice model to build local health workforce capacity.**

### **National Initiative to Strengthen Collaboration between HIV-TB through e-learning (e-NISCHIT) in India**

U Agarwal,<sup>1</sup> National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India.  
e-mail: upasna.ag@gmail.com

In 2017, the national AIDS and TB programs introduced conceptual changes in TB guidelines, wherein TB treatment for PLHIV was shifted from TB to HIV clinics. Initial experience pointed towards a countrywide need for mentoring of HIV teams in clinical and programmatic management of TB. An HIV-TB ECHO program, e-NISCHIT, was started in 2018, in collaboration with Government of India, CDC, Share India and ECHO India. National Institute of TB is the hub for this program and state run HIV Clinics from two states each of North and South India (~100 clinics) were selected to be the initial spokes. This program has successfully conducted 52 sessions to date, enabling rapid percolation of TB/HIV guidelines and handholding of peripheral HIV teams to undertake optimal TB management. The GOI has recently extended this program to areas with high prevalence of both HIV and TB in India's northeast and plans to expand nationwide.

### **Ensuring quality TB and specialty care for underserved patients**

M Buziashvili,<sup>1</sup> National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia.  
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Despite universal access to tuberculosis (TB) diagnosis and treatment in Georgia, TB services in rural and underserved areas of the country are still unevenly distributed; there is a lack of access to multi-disciplinary and specialty care, as well as to the latest updates and innovations in TB diagnosis, patient care and treatment. As a result, the majority of TB patients are referred to the central TB treatment facility to receive quality TB and specialty care.

To overcome the challenges of delayed treatment initiation and minimize time and costs of patient travel to central facilities, Project TB-ECHO was implemented in late 2017 and fully functional since early 2018.

Over 800 patient cases have been discussed since ECHO implementation which gives the country a hope to soon have a significant improvement in the number of lost to follow-up cases, increased treatment success and enhanced capacity of human resources on all country levels.

### **Building a Community of Practice for TB Program Managers - Utilizing the ECHO Model**

D Fortune,<sup>1</sup> National TB Controllers Association, Santa Fe, United States. e-mail: dfortune@tbcontrollers.org

The National Tuberculosis Controllers Association (NTCA) is the premier organization in the United States representing tuberculosis (TB) public health programs; NTCA has evolved as a non-profit, professional member service organization and has over 600 members from every state, city, and territorial TB program. NTCA wanted to enhance networking and educational opportunities to meet the unique needs of TB program managers responsible for overall program administration.

The NTCA launched its first Community of Practice session on July 11, 2019 with 56 participants from across the United States. The initial sessions (296 participants) focused on writing and preparing the CDC TB Cooperative Agreement 2020 Notice of Funding Opportunity. Series Two, (161 total participants) focused on writing the CDC Cooperative Agreement Five Year Progress Report. Series Three, (237 participants) focused on the maintenance of TB programmatic and clinical activities despite the pressing COVID-19 responsibilities added to TB programs.

### Expansion of the Regional TB ECHO Program across Central America

D Forno,<sup>1</sup> <sup>1</sup>CDC Central America Regional Office, Guatemala, Guatemala. e-mail: xan1@cdc.gov

The CDC Central America Regional (CAR) Office provides technical assistance to Ministries of Health in the region through a PEPFAR funded TB/HIV program. In 2019, WHO reported 14,353 TB cases in CAR including 1123 cases of TB/HIV in the region of seven countries.

Some of the challenges faced to obtain TB epidemic control in rural areas are lack of resources, poor referral of patients for care and treatment, difficult to reach communities and lack of specialized trained physicians to treat TB. From 2018-2019, CDC CAR launched three TB ECHOs in Guatemala, Panama and Honduras. The TB ECHO program in Guatemala included a 6-month TB basics national certificate program and trained around 300 healthcare workers.

In addition to the national programs, CDC CAR and its partner SE-COMISCA (Commission of Ministries of Health in the region) launched a regional program in May 2020 to discuss common challenges for all countries such as TB cases in immigrants, people living with HIV, diabetes and COVID-19.

### Advancing Prevention in Massachusetts, USA - Implementing the ECHO model to increase latent tuberculosis infection testing and treatment in primary care

D Szkwarko,<sup>1</sup> <sup>1</sup>Warren Alpert School of Medicine, Brown University, Providence, United States. e-mail: szkward@gmail.com

In 2016, the US Preventive Services Task Force updated recommendations to support latent tuberculosis infection (LTBI) testing as a preventive strategy and recommended that primary care providers (PCPs) integrate LTBI management into their primary care practices. PCPs rarely receive sufficient LTBI training and feel uncomfortable prescribing rifampin and isoniazid. In 2019, the Massachusetts (MA) Department of Health partnered with the University of MA Project ECHO hub to design a LTBI ECHO.

The course incorporates six virtual telementoring sessions for MA PCPs. A mixed-methods program evaluation was conducted. Pre- and post quantitative structured surveys were administered to LTBI ECHO course participants.

Qualitative in-depth interviews were conducted with participants and content experts to assess resulting practice changes and recommendations.

We found that our LTBI ECHO course increases PCPs knowledge and confidence and supports practice change. Health departments may find LTBI ECHO programs to be an effective intervention to train PCPs in LTBI management.

### SP-26 Leveraging a multiplex platform for TB, HIV and coronavirus for diagnostic testing and clinical monitoring: country experiences

#### Authorized service provision for GeneXpert through KNCV in Nigeria: shifting GeneXpert network from a TB diagnostic network to a multiplexed network with sufficient capacity

P Ajiboye,<sup>1</sup> <sup>1</sup>KNCV Tuberculosis Foundation, Abuja, Nigeria. e-mail: prisca.ajiboye@kncvtbc.org

The vast majority of the 407 GeneXpert machines installed across Nigeria were originally placed solely for the diagnosis of TB. Additional test menus have since been adopted for use on the available instruments such as HIV, Hepatitis B and C Viral load, EID, HPV amongst others. Most recently the instruments are adding the Xpert Xpress SARS-CoV -2 cartridges to the test menu for the diagnosis of the novel corona virus as this is the most accessible method for use in testing for COVID in Nigeria.

As other test menus come aboard the GeneXpert network, it is important that TB diagnosis is not pushed aside at the cost of TB patients and communities.

### The National TB program of the Kyrgyz Republic response to the COVID-19 pandemic

E Abdrakhmanova,<sup>1</sup> <sup>1</sup>The Kyrgyz Scientific Research Institute of Tuberculosis, TBC, Kyrgyzstan. e-mail: elmiraa1@yandex.ru

The Ministry of Health (MoH) of the Kyrgyz Republic organized a coordination body to manage a COVID-19 response with the TB and HIV management teams. The government, with WHO support, developed a comprehensive plan with salary increases for health care workers involved in testing and treatment of patients with COVID-19. The MoH endorsed the guidelines on COVID-19 management with inclusion of TB management. The NTP approved distribution of TB drugs for 14 days with VideoDOT. The MDR-TB department of the NTP for 30 patients was redesigned for patients with COVID-19. They procured medical, prevention and infection control equipment for management of patients with COVID-19. In the lockdown period, the UNDP, NRCS and NTP provided cars for distribution of TB drugs. Laboratory specialists from the NRL formed part of COVID-19 mobile teams. The NTP in collaboration with the HIV center prepared a proposal to the Global Fund on COVID-19.

## **How the Rwandan National Reference Laboratory (NRL) rearranged its Multiplex PCR capacity to meet the huge COVID-19 testing demand**

A Kabanda,<sup>1</sup> <sup>1</sup>NRL/Rwanda Biomedical Center, Kigali, Rwanda. e-mail: anyaruhirira@msh.org

Building on influenza surveillance and Ebola diagnostic capacity, the Rwandan NRL started COVID-19 testing by January 2020 for passengers from China. By March 2020, when the first COVID-19 positive was detected, the NRL tested 1000 samples (average 23 per day) which was manageable.

However, detection of the first patient alerted the Rwandan Ministry of Health to initiate new measures including isolation, tracing and testing for contacts as well as expanding laboratory testing for passengers arriving from countries where COVID-19 were reported. These measures increased the COVID-19 samples tenfold. Samples increased to 1500 samples per day from April 2020 onward. To achieve such demand, a strong coordination including laboratory capacity rearrangement was employed.

While the COVID-19 laboratory testing capacity was met, other services for TB and HIV were profoundly affected. The success to COVID-19 laboratory testing demand, challenges, disruption of others services, and future perceptive will be discussed.

## **SYMPOSIA: FRIDAY 23 OCTOBER 2020**

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### **SP-27 Exploring existing and potential uses of artificial intelligence for TB programming**

#### **Geographic TB risk profiling: real-time geospatial electronic case-based surveillance of TB active case finding in Pakistan**

M Potgieter,<sup>1</sup> <sup>1</sup>EPCON, Cape Town, South Africa.  
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Although tuberculosis (TB) continues to affect us all, it is predominantly a disease that disproportionately impacts certain geographic and risk communities greater than others. External factors such as climate, population density, urbanity and geographic location are known to have an effect on disease transmission and burden, but how do we create the evidence to support these probably causal relationships for TB? And how does that help us in understanding the subnational variations in TB risk?

This presentation addresses how a predictive model for subnational TB risk, grounded in a Bayesian framework, helps us to discover the unknown unknowns to unlock TB case detection and to optimise TB programme steering. Early outputs of subnational TB risk variation from the use of the model in several districts of Pakistan will be presented.

#### **Reinforcement learning to support public health decision making and optimize geographic allocation of diagnostic resources**

P Libin,<sup>1</sup> <sup>1</sup>University of Hasselt, Brussels, Belgium.  
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Maximizing efficiency of preventive public health strategies is an essential part of the response to infectious disease epidemics. To properly understand epidemiological processes, and to study emergency scenarios, epidemiological models that enable us to make predictions and to study the effect of prevention strategies in simulation are necessary. As the development of prevention strategies remains challenging, it is important to study how optimization techniques can be used to support decision makers. To this end, reinforcement learning approaches can help us to determine optimal prevention strategies. We discuss different reinforcement learning approaches, from multi-armed bandits to deep reinforcement learning, and discuss how these methods can be used to assist decision makers in the context of pandemic influ-

enza. Finally, we conclude to look at the potential of use these methods to optimally locate GeneXpert machines to serve the population TB and COVID-19 diagnostic needs.

### **Using Optimization and Heuristic Algorithms to Improve Diagnostic Networks and Sample Referral System Design**

S Rupani,<sup>1</sup> <sup>1</sup>LLamasoft, Cape Town, South Africa.  
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This presentation will discuss how optimization software, such as LLamasoft's Supply Chain Guru, and a recently developed open-access tool can help improve the design and performance of diagnostic networks and specimen referral systems. Country examples will be given across Kenya, Tanzania, Philippines, India etc. and topics will include key questions that this type of software can address (machine placement in existing facilities, optimal locations for new facilities for machine placement, and specimen transportation system), necessary data to input into the software, potential improvement in performance, challenges and limitations, and the shift from design to implementation.

### **Tuberculosis and COVID-19 cough pattern recognition using artificial intelligence**

R Pathri,<sup>1</sup> <sup>1</sup>Docturnal Private Limited, Hyderabad, India.  
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Docturnal's cough screening app for detection of pulmonary tuberculosis (TimBre) based on a machine learning algorithm, shows a sensitivity of 80% and specificity of 92%, updated from recent trial results and cross validated against GeneXpert and CXR.

The underlying training data covered a wide spectrum of labelled lung based cough including asthma, COPD, PTB, DRTB, PLHIV & TB, empyema, emphysema and controls across both the genders. TimBre's existing infrastructure for a smartphone with a built in microphone naturally extends to screen for ncovid19, and has been repurposed using existing Pneumonia cough sounds & also by obtaining annotated ncovid19 cough sounds.

This presentation will present up-to-date results on the sensitivity and specificity of the app, which currently stands at around 79% and 87% respectively and is undergoing a global pilot.



### **SP-28 My care, my metrics: why patient definitions of person-centred care are critical**

#### **Why we need a patient led and person-centric solution in TB**

M Pai,<sup>1</sup> <sup>1</sup>McGill University, Montreal, Canada.  
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This presentation talks about the need for patient led models of person centric care. It examines the relevance of this approach for large populations at risk globally, especially those most vulnerable and how to best cater to them, based on examples and case studies. It examines this by looking at current challenges that need to be addressed through such models in global approaches to stemming the TB epidemic.

#### **A Patient's Definitions of Care: Challenges and Opportunities**

A Ashesh,<sup>1</sup> <sup>1</sup>Survivors Against TB, Delhi, India.  
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This presentation draws on the presenter's experience as a TB patient and using this lived experience identifies the systemic, treatment, economic and personal challenges that patients face in accessing appropriate care. In doing so, it seeks to identify the key challenges that patients and communities at risk face and how understanding these perspectives gives opportunities to define high quality care that the health system ought to provide to patients.

#### **Community and patient participation in defining health needs and health policy: What does TB need?**

A Daftary,<sup>1</sup> <sup>1</sup>York University, Toronto, Canada.  
e-mail: adaftary@yorku.ca

This presentation illustrates significant approaches to participative approaches to defining health needs and using it to inform policy. It compares participation and community led models of communities making and defining quality of care across diseases and in different countries. In doing so it seeks to draw lessons for enhancing community and patient participation in identifying needs and the framing of policies and interventions for defining TB care.

### **A model of care from a survivor's perspective: Key Elements**

S Rane,<sup>1</sup> <sup>1</sup>Survivors Against TB, Mumbai, India.  
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This presentation seeks to present some fundamental aspects that a patient and community-led model of person-centered care must include.

The presenter draws on presented challenges and opportunities, his experiences as a TB survivor, and sketches out the key elements that community and patient-led models of care must include.

### **SP-29 TB in pregnancy: what's new in prevention and treatment?**

#### **Controversies of TB Prevention during Pregnancy**

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Pregnant and post-partum women are at increased risk of contracting TB disease, particularly in the context of HIV-coinfection. Morbidity is often severe, with adverse maternal, pregnancy and infant outcomes. TB preventive therapy (TPT) is effective in preventing TB disease in women living with HIV, but there are concerns about the risks and benefits to both mother and fetus of TPT during pregnancy. Regimen choice and the optimal timing and duration of therapy to maximize benefits and safety are also unclear. Decisions may be context-specific depending on TB and HIV prevalence and national screening, diagnostic and treatment practices.

Current evidence and outcomes of TPT in pregnancy and the postpartum period are summarized and the challenges discussed.

#### **3HP, a new option for TB Prevention during Pregnancy?**

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Pregnancy increases the risk of progressing from latent tuberculosis infection (LTBI) to active TB. A recent randomized controlled trial reported increased risk of adverse pregnancy outcomes in women with HIV who initiated isoniazid preventive therapy during pregnancy versus in the postpartum period.

These results have left national and international programs at a loss for what to recommend for TB prevention in pregnant women at high risk of developing active

TB. IMPAACT 2001 was a multi-site Phase I/II study evaluating the pharmacokinetics and safety of 3HP among pregnant women with or without HIV.

In this talk, the results of this important study and its implications for antenatal policies will be presented.

### **The short bedaquiline regimen in pregnant women with RR-TB: treatment, pregnancy and infant outcomes**

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The South African Medical Research Council (MRC) studies an ongoing cohort of pregnant women with RR-TB. We previously reported maternal treatment, pregnancy and infant outcomes in the first 108 women enrolled, comparing outcomes in the injectable versus bedaquiline containing regimens.

We now report maternal treatment, pregnancy and infant outcomes at 6 months in 18 women treated with the short (9–12 month) bedaquiline regimen. Sixteen (89%) of the women were co-infected with HIV and on ART, the median age was 28.5 years. Thirteen (72%) have successfully completed treatment. Of 16 babies born, 4 (25%) were premature and 5 (31%) low birth weight (<2500g). There were no foetal or neonatal deaths. Eleven babies have been clinically assessed at 6 weeks, all are thriving (following the normal growth trajectory) and achieving their developmental milestones timeously. Pregnant women treated with the short bedaquiline regimen have similar treatment outcomes to non-pregnant adults. All who have delivered have healthy babies.

### **Innovative research study designs on TB in pregnancy: challenges and solutions**

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The risk of developing TB for a woman is highest during pregnancy and the early postpartum period. Unlike non-pregnant adults, we have a poor grasp of best practices for screening, diagnosing and preventing TB in pregnant women. Pregnant women need to be followed from pregnancy through delivery and postpartum to understand the immunological dynamics during this period. A significant challenge is enrolling and retaining pregnant and postpartum women.

Since 2016, we have conducted an observational cohort study of HIV-infected and –uninfected pregnant women with latent TB infection (PRACHITi) to improve our understanding of the intersection of TB and pregnancy immunology.

In this talk, the results of PRACHITi will be presented as well as strategies employed to maintain >90% retention rate for 12 months postpartum.

### **SP-30 Towards a TB-free childhood: best practices to find, cure and prevent TB in children in Africa.**

#### **Finding missing pediatric TB cases through facility-based intensified case findings: lessons learnt from CaP TB project in Malawi**

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Diagnosis of pediatric TB remains challenging and results in a significant case detection gap. The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) partnered with National TB control program in Malawi to implement the Unitaid funded CaP TB project, aimed at improving childhood TB diagnosis and prevention.

The project rolled-out a comprehensive case finding intervention in 16 purposively selected sites in six districts. Sites received training on screening and diagnosis of pediatric TB, support for pediatric-specific symptom screening of children in various entry points, increased access to Xpert MTB/RIF testing through strengthened sample collection and transport and support for access to CXR.

Improvement of pediatric TB case finding has been assessed using a pre-post intervention design. Prospective data have been collected starting from first quarter 2019.

The presentation will review early evidence generated by the project as well as key lessons learnt that can inform successful implementation of childhood TB interventions.

#### **Household Outreach and patient-centered engagement to increase child and adolescent TB and HIV case finding (HOPE project in south western Uganda)**

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In a Ugandan district with the lowest TB case notification rate, we conducted household-based TB contact tracing. We evaluated TB and HIV case finding, and linkage. Community health workers and HIV testing volunteers screened household contacts for TB and HIV. Presumptive TB cases provided diagnostic specimens or were referred for specimen collection.

Contacts <5yrs and PLHIV without TB were offered IPT. Out of 1592 household members, 197 had a positive TB screen and 16 new TB cases (8.1%) were identified (4, 25% were children <15yrs). Ten (2%, 10/499) new HIV patients were identified (5, 50% were children <15yrs) and linked to ART. Of the 429 contacts with negative TB screen, 375 were eligible for IPT, 279 initiated IPT (85.8%) and 195 (69.9%) completed IPT.

Household-based contact tracing using low-cadre health workers is feasible and contributes to finding TB and HIV cases especially among children who may otherwise be missed.

### **Catalysing the introduction of child-friendly formulations of medicines for Drug-Resistant TB: Lessons learned for new formulations and regimens in the pipeline**

B Waning,<sup>1</sup> <sup>1</sup>Stop TB Partnership, Geneva, Switzerland.  
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The presentation will focus on the key steps STBP/GDF took, in collaboration with implementing and technical partners, and lessons learned to catalyze adoption of child-friendly formulations of DR-TB medicines by programmes.

These key steps include identifying and consolidating demand from early adopter programmes, using the consolidated demand to negotiate price and supply terms for these formulations, funding the initial procurement for early adopter programmes and using a pooled procurement approach to meet minimum order quantities and batch sizes, and monitoring implementation and promoting sustainability. Globally, STBP/GDF provided more than 1000 treatment courses of child-friendly formulations, nearly double the estimated number of children less than 5-years old treated annually.

Lessons learned on the benefits of an integrated approach to new tool introduction, from in-country demand generation through upstream supply security and how these can apply to new child-friendly formulations and regimens in the pipeline will be shared.

### **Development of a DHIS-2 Smart Application for Data Collection and Decision Making for Use by Community Health Workers doing Household-Based TB Contact Tracing in Uganda**

S Kununka,<sup>1</sup> <sup>1</sup>Health Information Systems Program Uganda (HISPUg), Kampala, Uganda.  
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Contact tracing is an important way to find new cases of tuberculosis (TB) disease as well as identify household members who might qualify for TB preventive treatment (TPT). This is especially important for finding at-risk children in high-burden countries (such as Uganda), where a significant number are otherwise “missed.”

Despite the importance of contact tracing, the reality is that contact tracing is challenging to implement and sustain due to the time, complexity, and human resources required.

This presentation will describe the development of a DHIS2-based smart application (“electronic TB contact

tracing tool”) to help address these barriers to contact tracing in Uganda. This application was developed to be a tool for community health workers to use while carrying out household-based contact tracing in resource-limited settings.

We will describe the development process for this application, describe how it was used, and offer some early end-user results and feedback.

### **Improving pediatric and adolescent TB case detection in Mozambique through an Xpert MTB/RIF®- and spatial parameter based stratified risk strategy (X-patialTB)**

B Saavedra,<sup>1</sup> <sup>1</sup>Tuberculosis at the Centro de Investigação em Saúde de Manhiça (CISM) and the Barcelona Institute for Global Health (ISGlobal), Barcelona, Mozambique.  
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The X-patial TB project aimed to increase the number of TB diagnosis in Manhiça district (MD), a high TB-HIV burden area in Southern Mozambique. This study was funded by TB-REACH and embedded in routine TB surveillance of the National TB Control Program in Mozambique.

The main objective was to determine the impact of an active case finding strategy, based on Xpert MTB/RIF Ultra semi quantitative results (as a proxy of index case infectiousness) and spatial parameters, on tuberculosis case notifications in the district of Manhiça (intervention area) and compare it to a control area in the District of Magde. This descriptive cross-sectional study took place from March 2018 to February 2019 and the target population size was 16748 TB contacts.

In this symposium, we will present the impact on the pediatric population, in whom a specific diagnostic algorithm was implemented to address the inherent difficulties of paediatric TB diagnosis.

## **SP-31 Challenges and issues in ensuring continuum of care for migrants crossing borders with TB.**

### **What we know or do not know about migrants who cross borders while still on TB treatment**

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To date there has been less focus on assuring continuity of care for non-immigrants who leave a country while on TB treatment, and few formal analyses have been published on TB patients who transfer-out of a country before treatment completion and the continuity of their care in destination countries. Understanding the volume of such patients and its global impact, and how countries manage TB patients who leave a country while on treatment would be foundational to the development of international standards and indicators for transfer-out patients. This presentation will share the results of a cross-country study that was jointly conducted by the US and Japan, which aimed to describe the basic epidemiology of TB patients who transfer-out, and the country-level practices of coordinating transfer-out, in selected countries.

### **US Centers for Disease Control and Prevention**

K Moser,<sup>1</sup> <sup>1</sup>US Centers for Disease Control and Prevention, Atlanta, United States. e-mail: kzm5@cdc.gov

In the US, 2-4% percent of persons diagnosed with active TB, transfer out prior to treatment completion. The US Centers for Disease Control and Prevention's Division of Global Migration and Quarantine provides linkage to destination countries and follow-up for TB patients that transfer out through the CureTB program.

This presentation will describe the work of CureTB, referral and outcome data, as well as elements that enhance success for mobile patients.

### **Bridge TB Care – the first step in bridging care and support for foreign-born persons with TB who are returning to countries of origin**

L Kawatsu,<sup>1</sup> <sup>1</sup>The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Kiyose, Japan. e-mail: kawatsu@jata.or.jp

While in Japan, approximately 1 in 10 of its foreign-born TB patients are “transferred-out” of the country prior to completing their treatment, there had been no coordinated support provided to such patients, to ensure continuum of care.

Following a national survey on the state of “transfer-out” of foreign-born TB patients, in May 2020, a project – “Bridge TB Care” - was launched by the Research Institute of Tuberculosis, to coordinate smooth transfer of TB treatment from Japan to countries patients are travelling to, and follow-up until the completion of TB treatment.

This presentation will discuss on the main findings of the national survey and present some of the early experiences of the Bridge TB Care.

### **Building regional consensus on minimum standards for continuum of TB care in SADC region**

I Chirime,<sup>1</sup> <sup>1</sup>ECSA-HC, Arusha, Tanzania, United Republic of. e-mail: mchirime01@gmail.com

Cross-border migration is a challenge to TB control in Southern Africa Development Community (SADC), with an estimated 5 million documented and 20 million undocumented migrants, and 500 thousand mine workers with high burden of TB, frequently migrating across countries. SADC member states endorsed political declarations and frameworks to harmonise TB management seven years ago, but there was insufficient implementation.

A recent assessment revealed that patients crossed borders without formal referrals, minimal to no documentation, no feedbacks, re-initiation of MDR-TB treatment with country-specific regimens. The SATBHSS project facilitated consensus and development of regional standards for TB continuum of care among 8 SADC countries: inter-country communication and M&E; cross-border referrals of DS and DR-TB; continuum of treatment with same regimens; integration of TB in existing cross-border surveillance platforms; integration of paper and electronic cross-border referral systems.

This presentation will describe the process of development, the standards, training and pilot.

### SP-32 Regional studies that are improving the zoonotic TB scientific evidence base.

#### A comprehensive ONE health approach to combat Bovine tuberculosis in Santa Catarina State - Brazil

E Anzai,<sup>1</sup> <sup>1</sup>Regional University of Blumenau - FURB, Blumenau, Brazil. e-mail: elanzai@hotmail.com

Bovine TB cases in humans often go undetected or misdiagnosed because current laboratory tests cannot differentiate the bacteria that causes bovine TB, leading to death or delayed treatment in patients. Dr. Anzai is assessing new diagnostic tests that will reduce cost, enable rapid detection and significantly aid in preventing transmission of bovine TB between animals and from animals to humans.

#### Surveillance of animal-adapted MTBC in clinical and bovine carcasses in Ghana: A call for active One-health approach for TB control

D Yeboua-Manu,<sup>1</sup> <sup>1</sup>The Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana. e-mail: DYeboah-Manu@noguchi.ug.edu.gh

The true burden of zoonotic tuberculosis (zTB) remains unknown, due to lack of specific diagnostics for distinguishing the animal-adapted variants from the human-adapted *Mycobacterium tuberculosis* complex. Furthermore, due to lack of funding and to some extent manpower, routine surveillance is not done.

My presentation will span from earlier screening activities we conducted with the veterinary services on herds from a tertiary research facility and from free-range, findings from the population-based molecular epidemiological study and an on-going study analyzing for mycobacteria among carcasses from selected slaughterhouses.

#### Defining genes essential for the survival of *Mycobacterium bovis* to identify novel therapeutic targets for Zoonotic TB

S Kendall,<sup>1</sup> <sup>1</sup>The Royal Veterinary College, London, United Kingdom. e-mail: skendall@rvc.ac.uk

Lineages of the MTBC are highly similar genetically yet show distinct host preferences. Several studies identifying the impact of sequence variation on differences in gene expression have provided useful insights into the differences between MTBC lineages.

However, studies examining the impact on sequence variation on the genetic requirements for survival have been limited to the human adapted lineages.

We are using TnSEQ in order to identify the genetic requirements for survival of the reference strain of *Mycobacterium bovis*. We have used the MycomarT7 phagemid system which inserts into permissive TA sites across the genome. Transposon insertions were randomly distributed throughout the genome and 34,178 out of a total of 73,536 TA sites contained insertions. CRISPRi interference has been successfully established in the laboratory and will be utilised to validate putative essential genes.

### SP-33 Role and contribution of algorithm and score for diagnosis of paediatric TB.

#### Overview of challenges in diagnosing TB in children and shortcoming of existing diagnostic algorithms and scores

J Oliwa,<sup>1</sup> <sup>1</sup>KEMRI-Wellcome Trust Research Programme-Nairobi, Nairobi, Kenya. e-mail: JOliwa@kemri-wellcome.org

Tuberculosis is believed to be a “hidden epidemic” in children, with approximately 65% cases missed each year worldwide. Kenya TB prevalence survey (participants >15yrs) revealed 75% of TB cases had presented to health facilities with suggestive symptoms but were never diagnosed. The proportion of younger children undiagnosed in Kenya is presently unknown, but is presumably as high. We explored TB diagnostic practices amongst paediatric admissions using a conceptualised care cascade based on Kenyan TB guidelines, and found more than half of all admissions met the initial criteria of two or more suggestive signs of TB, but less than 3% got a TB differential diagnosis and few had TB diagnostic tests done.

We need a better understanding of which children may have TB and how they present, with clearer guidelines to help clinicians better select which patients to investigate, how to interpret test results and when to make a clinical diagnosis.

### Methodological challenges and alternative in the evaluation of tuberculosis diagnostic algorithms in children

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Mycobacterial culture, the reference standard to evaluate new diagnostics and diagnostics algorithms in adults, has a much lower sensitivity in children. A significant proportion of children enrolled in prospective studies do not have bacteriological confirmation and exclusion of TB is more difficult. The shortcomings of the reference standard are more pronounced in younger children, who have a different spectrum of clinical presentation and are less able to produce sputum samples.

Although the absence of a robust reference standard is challenging, alternatives methods utilising standard case definitions and treatment decision algorithm also present limitations. Several attempts are being made to incorporate systematic screening steps into the diagnostic algorithm in adults.

The presentation will describe how some of these algorithms have potential to improve diagnostic approaches in children.

### New tuberculosis diagnostic algorithm/score for vulnerable children: children with HIV infection and children with severe acute malnutrition

O Marcy,<sup>1</sup> <sup>1</sup>University of Bordeaux, Bordeaux, France.  
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Numerous scoring systems have been developed to help standardize tuberculosis diagnosis in children but their heterogeneity, lack of validation, and poor performance in HIV-infected children was a major limitation to their use in routine practice. PAANTHER was the first study developing a diagnostic score exclusively in HIV-infected children, using methods recommended for diagnostic prediction models. The score, based on clinical and chest-radiograph features, Xpert MTB/RIF results, and abdominal ultrasonography, has an overall sensitivity of 89%, and a specificity of 61%, and could enable standardized treatment initiation in most HIV-infected children with tuberculosis, used within a step-by-step algorithm. The PAANTHER TB treatment decision algorithm is currently being implemented and tested in an external validation study, the TB-Speed HIV study.

The ongoing TB-Speed SAM study is also aiming to develop a similar score in hospitalized children with Severe Acute Malnutrition, another vulnerable population at high risk of underdiagnosis.

### Performance of new screening and diagnostic tests in potential pediatric tuberculosis diagnostic algorithms: interim results from the RaPaed study

N Heinrich,<sup>1</sup> <sup>1</sup>Ludwig – Maximilians – University, Munich, Germany. e-mail: heinrich@lrz.uni-muenchen.de

The RaPaed – TB study is evaluating a number of new, child – friendly candidate diagnostic tests, funded by EDCTP. Samples used include (fingerprick) blood, urine and stool.

The study completed 50% of recruitment (400 children) in February 2020, and interim analysis results will be presented. Using more than one new tests, an algorithm of screening and confirmatory new test may be possible, with a low-cost and accessible screening test, and a confirmatory test that may be more complex.

### Contribution of chest X-ray in the paediatric diagnostic algorithm?

J Seddon,<sup>1</sup> <sup>1</sup>Imperial College London, Cape Town, South Africa. e-mail: james.seddon@imperial.ac.uk

Chest x-rays (CXRs) are commonly used in the evaluation of children with suspected TB and yet, even after decades of use, it is unclear which children should be investigated with CXR and if CXR is used, where it should be placed in the diagnostic algorithm. In many high TB-burden settings, access to CXR is challenging, the quality of the images is poor, interpretation is difficult and there is an associated cost for families.

In this talk, there will be discussion of which children should be evaluated with CXR and new development that could make it easier to use CXR in high burden and resource limited settings for the diagnosis of TB in children will be presented.

## **SP-34 Human rights and tobacco – progress and next steps for protecting populations from tobacco industry interference in child health.**

### **Human Rights based approach as the pathway for protecting populations from tobacco industry: global progress and next steps**

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A human rights approach to ending the tobacco epidemic is unique; it frames freedom from smoking addiction and health harms from tobacco use as a human right and requires governments to advance human development by implementing measures that decrease use. The Framework Convention on Tobacco Control (FCTC) has brought significant progress in advancing health, but lacks enforcement mechanisms. Using human rights obligations forces the hands of governments, empowers tobacco control advocates, brings new allies and suggests innovative policy solutions.

This presentation will discuss both top-down and bottom-up approaches and illustrate the progress that is being made by advocates around the world. Bottom up approach involves human rights mechanisms to advance tobacco control by engaging in the reporting processes associated with national human rights treaty obligations. The global top down approach integrates tobacco control objectives among global human rights bodies, as well as collaboration among health and human rights mechanisms.

### **Human rights reporting and campaigning on tobacco use and imported tobacco in Germany**

L Graen,<sup>1</sup> <sup>1</sup>Consultant, Berlin, Germany.  
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Germany has not implemented key tobacco control policies and politicians often portray tobacco as an individual lifestyle choice rather than an issue that needs government regulation. By framing tobacco control as a human rights and children's rights issue and using human rights reporting mechanisms, civil society puts pressure on the German government to implement regulatory measures. In 2018, Unfairtobacco started to build the German Network for Children's Rights and Tobacco Control, bringing actors from different backgrounds together that had no links to each other before: organizations in public health, human/children's rights and development. Because human rights treaties have enforcement mechanisms that are lacking in the FCTC, this angle advances tobacco control advocacy in Germany.

With this presentation, we aim to share our experience and thereby build the capacity of colleagues on how to use human rights arguments and reporting processes to advance tobacco control in their countries.

### **Reclaiming child rights to health by preventing the tobacco industry from using disruptive tactics to deny rights to be tobacco-free**

A Jones,<sup>1</sup> <sup>1</sup>The Union, Sydney, Australia.  
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The denial of children's rights is at the heart of the tobacco industry's interference in health policies. Five of the largest tobacco companies control 80% of the global market, and mergers and acquisitions have solidified interference on an industrial scale. Driven by shareholder demand for profits, the industry needs children to replace the sick, the dying and those that have quit.

With no apparent intention of ending their marketing of addictive, lethal products, which kill 8 million people a year, the industry is aggressively releasing new products and using front groups, corporate social responsibility and philanthropy to disrupt tobacco control. While the interference tactics of Big Tobacco are well documented, their misleading concerns about children (while simultaneously denying their rights) demands a more strategic response, with integrated use of treaties and frameworks to protect children.

### **Child Labour in tobacco: a violation of Human Rights and national law in Bangladesh**

S Alam,<sup>1</sup> <sup>1</sup>The Union, Dhaka, Bangladesh.  
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The exploitation of children as labour in tobacco manufacturing is a major problem as both a violation of Human Rights and the national law in Bangladesh. Avenues to counter child labour exist and will be reviewed along with challenges and opportunities to do more to protect children from tobacco and tobacco industry interference.

## **SP-35 Migration journeys and the risk for TB – what do we know and what do we need to find out?**

### **Migration routes and their health hazards**

D Zenner,<sup>1</sup> <sup>1</sup>Queen Mary University, London, United Kingdom. e-mail: d.zenner@qmul.ac.uk

This talk will focus on common routes of migration with evolving patterns of health hazards en route, in detention, and access to basic services and healthcare.

It will set the scene to gain better understanding about differential TB epidemiologies within the context of migration.

### **IOM's Migration Health Assessment Programmes**

C Gilpin,<sup>1</sup> <sup>1</sup>International Organization for Migration (IOM), Geneva, Switzerland. e-mail: cgilpin@iom.int

Migration health assessments (MHAs) are one of IOM's most well-established migration management services. At the request of receiving country governments, IOM provides migrants with physical and mental health evaluations for the purpose of assisting them with resettlement, international employment, obtainment of temporary or permanent visas, or enrolment in specific migrant assistance programmes.

This presentation will outline the MHAs and how the clinics and TB laboratories have been re-purposed in the context of the COVID-19 pandemic.

### **Influence of the migration route on TB epidemiology in Israel – PH Tel Aviv**

Z Mor,<sup>1</sup> <sup>1</sup>Tel Aviv Department of Health, Ministry of Health, Tel Aviv, Israel.  
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This talk will review the TB epidemiology of Israel-bound migrants from the horn of Africa, comparing those who were airlifted from Ethiopia and those who made a land journey from Eritrea or Sudan.

This talk will use screening and follow up data from the Israeli programmes, which screened almost 200,000 persons over several decades.

## **How can we make TB screening for migrants patient-centred? (Dr Matt Burman and Dr Jess Potter)**

M Burmann,<sup>1</sup> <sup>1</sup>Queen Mary University, London, United Kingdom. e-mail: m.burman@qmul.ac.uk

The talk will be co-presented by Matt Burman and Jess Potter. It will consider whether our current models of care for TB screening provide a patient-centred approach for migrants and what impact this has on patient experience and health outcomes.

The talk will take both a patient-perspective using recent research in India to understand access to TB screening along the migratory journey to the UK and a programmatic-perspective using data from a community based LTBI screening and treatment programme in East London.

### **Influence of the migration route on TB epidemiology – how the TB incidence of Netherlands-bound migrants compares**

G De Vries,<sup>1</sup> <sup>1</sup>National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands.  
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This talk will provide an overview of descriptive epidemiology of TB in migrants in relation to their duration of stay in the Netherlands. It will show the dynamics of migrants developing TB. In 2019, one out of six patients in the Netherlands was born Eritrean, and almost all came to the Netherlands as an asylum seeker.

The talk will also demonstrate the use of whole genome sequencing in identifying pre-migration outbreaks. Lastly, the talk will discuss interventions to early identify and prevent TB in different migrant groups.



## SP-36 Human-centred design to advance patient-centred TB care in low-income countries

### Human-Centred Design: A Designer's Perspective on Innovation for Action in Global Health

M Kreger,<sup>1</sup> <sup>1</sup>IDEO.org, San Francisco, United States. e-mail: mkreger@ideo.org

IDEO.org is a nonprofit design studio that designs products and services alongside organizations that are committed to creating a more just and inclusive world. This presentation will describe IDEO.org's approach to designing for change in resource-constrained settings, sharing learnings from across the global health portfolio while highlighting the potential role design-led approaches can play in creating patient-centered innovations for TB care. The presentation will highlight successes and failures of the design process as it was applied to reimagining the TB patient and family experience in Uganda, and will explore how design-led approaches might help accelerate the creation and adaptation of proven health interventions in Uganda, and beyond.

### Adapting Digital Adherence Technology (DAT) for TB Treatment using Human-Centered Design in Uganda.

C Berger,<sup>1</sup> <sup>1</sup>University of California, San Francisco, San Francisco, United States. e-mail: Christopher.berger@ucsf.edu

Tuberculosis treatment success rates in Uganda are lower than in many other high burden countries. The goal of this TB REACH-funded project is to make TB treatment more convenient for patients by enabling them to take medicines when and where they choose, instead of having to be observed taking medicines by a health worker.

This presentation will describe the process of adapting 99DOTS, a low-cost DAT, to better fit user needs using human-centred design, and user engagement and satisfaction with the contextually-adapted 99DOTS platform following its roll-out at 18 TB treatment units across Uganda.

### Increasing TB case detection in Nigeria using Human-Centred Design to simplify referrals from medicine stores.

J Edor,<sup>1</sup> <sup>1</sup>Breakthrough ACTION Nigeria, Utako Abuja, Nigeria. e-mail: joseph@ba-nigeria.org

Tuberculosis (TB) case detection rates in Nigeria are among the lowest globally and have persisted for several decades. Many people with TB struggle to find the

correct diagnosis and cure for their cough; some spend months going from one medical vendor to another, eventually seeking help from traditional herbalists and/or religious leaders. Breakthrough ACTION Nigeria and the Nigerian National Tuberculosis and Leprosy Control Programme conducted a formative assessment, funded by USAID, to understand factors contributing to low-TB case detection in Nigeria with the aim of designing Social and Behaviour Change (SBC) interventions to increase TB case detection.

This presentation will describe Breakthrough ACTION's use of the SBC Flowchart method, which integrates social science research, human-centred design (HCD) and communication into a cohesive, flexible approach. The preliminary findings from a 12-week pilot suggested the number needed to test to find a case is 6, compared to the national figure of 9.

### Human-Centred Design to Improve Delivery of TB Contact Investigation in Uganda

J Davis,<sup>1</sup> <sup>1</sup>Yale School of Public Health, New Haven, United States. e-mail: lucian.davis@yale.edu

WHO recommends that contact investigation of index TB patients be routinely performed in low- and middle-income countries for TB case-finding and prevention, but acceptance, completion, and yields remain low.

The goal of this project is apply human-centred design to adapt household contact investigation to improve its yield by prioritizing the needs and experiences of index TB patients and their close contacts in Kampala, Uganda.

This presentation will compare and contrast our experiences using human-centred design and conventional behavior-change approaches to implementation, and identify metrics that can be used to assess the impact of human-centred design on patient and public health outcomes.

### **SP-37 Strategies for addressing barriers for LGBTQIA in accessing high quality TB care - a comparative analysis with HIV.**

#### **Barriers LGBTQIA persons face in accessing HIV care: Lessons for TB**

G Yadav,<sup>1</sup> <sup>1</sup>Humsafar Trust, Delhi, India.  
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This presentation will identify the barriers faced by LGBTQIA in accessing HIV care and examine why these barriers exist. It will also throw light on the systemic exclusion of LGBTQIA persons from programs meant for them. It will identify clear systemic barriers and challenges and how these affect the health and well-being of these populations. It will also examine how to address these barriers and exclusion in the context of TB care.

#### **A health systems and medical perspective on providing HIV care to LGBTQIA persons and the lessons for TB**

A Tomson,<sup>1</sup> <sup>1</sup>Independent, Cape Town, South Africa.  
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This presentation will identify the gaps in the health system that create challenges for doctors in providing quality HIV care to LGBTQIA persons. It will talk about the impact of medical abuse on LGBTQIA persons. It will look at how the health system address the medical abuse faced by LGBTQIA persons.

It will examine, by drawing lessons from the HIV experience for TB care, the role of health systems, medical community and sensitisation in providing quality care to LGBTQIA affected by TB.

#### **The Indian and South African Experience of legal activism on LGBTQIA right to health - lessons for TB care**

J Kothari,<sup>1</sup> <sup>1</sup>Centre for Law and Policy Research, Bangalore, India. e-mail: jayna.kothari@clpr.org.in

This presentation will examine the role of legal activism in securing a better realisation of the right to health and resultantly better quality care for LGBTQIA persons. It will engage in a comparative analysis of current and previous efforts in legal activism on LGBTQIA right to health and quality in India and South Africa in contexts such as HIV, identifying the gaps, challenges and best practices. It will conclude by drawing lessons for making TB care more inclusive and effective in addressing rights based barriers to health for LGBTQIA persons, especially in high burden TB countries.

### **SP-38 Hidden, but for how much longer? The epidemiological and economic burden of post-TB.**

#### **Post-tuberculosis lung disease at the bedside**

B Allwood,<sup>1</sup> <sup>1</sup>Stellenbosch University, Cape Town, South Africa. e-mail: brianallwood@gmail.com

This talk will begin with the definition of post-tuberculosis lung disease (PTLD), highlighting the strengths and limitations of the currently proposed definition. It will then describe a clinical classification of PTLD and explain areas of complexity which can hamper measurement of PTLD using single instruments (e.g. spirometry alone).

The talk will use case studies of patients with PTLD as illustrations suitable for both non-clinicians and clinicians not familiar with the management of PTLD. Difficulties in clinical management of such patients will be briefly mentioned.

#### **How many TB survivors are there alive today?**

P Dodd,<sup>1</sup> <sup>1</sup>University of Sheffield, Sheffield, United Kingdom. e-mail: p.j.dodd@sheffield.ac.uk

We estimate the number of people alive in 2020 who have survived TB since 1980. We focus on those who have received treatment for TB (including restricting to those who have received treatment within the last 5 years), but also estimate the number of survivors whose TB went untreated.

We report results by age, sex and HIV status at the WHO regional level and global level. To do this, we created post-TB life-tables by adapting UN life tables for each country and sex to single calendar years and ages, separating out HIV-specific mortality and applying hazard ratios for increased mortality among TB survivors. We applied these life-tables to interpolated WHO data on new TB notifications accounting for deaths on treatment. To estimate the number of survivors of untreated TB, we applied our post-TB life-tables and TB case fatality rates to WHO estimates of the gap between notifications and incidence.

#### **Estimating the global morbidity and mortality burden of post-tuberculosis**

N Menzies,<sup>1</sup> <sup>1</sup>Harvard University, Boston, United States. e-mail: nmenzies@hsph.harvard.edu

Estimates of the global burden of TB have focused on the morbidity associated with prevalent TB disease, and the years of life lost due to death during the disease episode.

In this analysis we estimate the additional burden of disease (years of life lived with disability, years of life lost, and disability adjusted life years) resulting from post-tuberculosis. We estimated these outcomes for the cohort of individuals that developed TB disease in 2018, as compared to a counterfactual of no TB disease. We estimated outcomes using a mechanistic model that simulated health outcomes over the lifetime, stratified by age, sex, HIV status, and MDR-TB status. We report results by country and regional groupings. Post-tuberculosis represents a substantial additional burden of disease caused by TB. These results provide additional motivations for TB prevention, and for limiting the accumulation of lung damage and other morbidity for those who do develop disease.

### **Estimating the economic burden of post-tuberculosis to the household**

S Sweeney,<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
e-mail: sedona.sweeney@gmail.com

Reduction of catastrophic costs due to TB is a key policy priority globally, but estimates of catastrophic cost currently assume costs are only incurred during the disease episode.

In this analysis we estimate patient- and household-incurred costs due to post-tuberculosis. We describe a framework of post-tuberculosis costs incurred by households, including direct medical, direct non-medical, and indirect costs. We estimate costs incurred to households for the cohort of individuals that developed TB disease in 2018 in selected countries. We describe preliminary estimates of costs and catastrophic costs incurred by TB-affected households across countries and by category.

### **SP-39 National TB prevalence surveys in Southern Africa: key results, lessons learned and programmatic implications**

#### **The road to TB elimination in Eswatini: who are we missing and why?**

W Sikhondze,<sup>1</sup> <sup>1</sup>Ministry of Health/National TB Control Program, Manzini, Eswatini.  
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Eswatini, a high TB/HIV burden country, successfully conducted its first national TB prevalence survey in 2018. Results showed a significant number of TB cases were being missed with the current symptom screening strategy. Innovative approaches are needed to guide the strategic direction for TB elimination against the high background of HIV.

This presentation will share the country's experience and the policy/programmatic implications of the survey findings.

#### **Lesotho national TB prevalence survey 2019: results, lessons learnt and implications for the national TB programme**

B Maama Llang,<sup>1</sup> <sup>1</sup>Lesotho NTP, Maseru, Lesotho.  
e-mail: maama36@hotmail.com

Lesotho, a high TB/HIV burden country, conducted a national TB prevalence survey in 2019 that was led by University Research Company jointly with its partners NEXT2PEOPLE and AQUITY Innovations.

The presentation will focus on the rationale for conducting the survey, methodology (including the use of Xpert Ultra – one of the first countries to do so), lessons learnt during implementation, key results (that included a high burden among men compared with women, a burden that increased with age, and a very large TB/HIV coinfection rate) and implications for the national TB programme.

#### **The first national TB prevalence survey of Mozambique, 2018-2019: challenges and achievements**

I Manhiça,<sup>1</sup> <sup>1</sup>Ministry of Health/National TB Control Program, Maputo, Mozambique.  
e-mail: ivanmca2004@yahoo.com.br

Mozambique is in all three WHO high burden lists for TB, HIV/TB co-infection, and multi-drug resistant TB. The country conducted its first national TB prevalence survey to gain more insight in the countries TB epidemic and used the results to guide TB control in the country. This presentation will discuss the methodological approach, key findings and lessons learned including how

to guide quality assurance in culture, and manage discordant results between Xpert MTB/RIF and culture. It will also underline key operational and technical challenges faced during the field work.

Finally, it will describe the impact of the survey results on the design of future strategies for TB control in Mozambique.

### **Estimating incidence from national prevalence survey results in Southern Africa**

P Glaziou,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: Glazioup@who.int

A presentation of statistical methods, key results and their limitations will be made, covering the following countries: Eswatini, Lesotho, Mozambique and South Africa.

### **SP-40 Implementation and scale-up of TB preventive treatment: overcoming challenges to reach people living with HIV**

### **TPT Scale-Up among Adults and Children Living with HIV: Best Practices from Uganda**

D Lukoye,<sup>1</sup> <sup>1</sup>Centers for Disease Control and Prevention, Kampala, Uganda. e-mail: oju0@cdc.gov

In 2019, Uganda established a task force to dramatically scale-up TPT through a coordinated, nationwide 100-day campaign to place all eligible adults and children with HIV on TPT. Because of the strong commitment from political leadership and the technical expertise of their task force, from August to October 2019 Uganda initiating 300,000 people on TPT and reached high levels of TPT completion for those initiating.

The Ugandan experience will be shared, including the importance of building the support needed to mobilize the campaign as well as executing procurement and supply chain logistics during rapid scale-up.

### **TPT Scale-Up among Adults and Children Living with HIV: Best Practices from Kenya**

C Wambugu,<sup>1</sup> <sup>1</sup>Ministry of Health, Nairobi, Kenya. e-mail: drcwambugu@gmail.com

After implementing an aggressive TPT scale-up effort, the number of people receiving TPT in Kenya increased 60-fold from just under 10,000 in 2014 to more than 600,000 in 2016. By December 2018, Kenya had provided

TPT to 85 percent of the one million Kenyans receiving ART. Since 2014, the number of new TB cases among people with HIV has fallen by 40 percent.

Kenya has achieved the highest proportion of eligible CLHIV receiving TPT in the region and has initiated 35% of eligible child contacts under five years of age on TPT, higher than regional averages. The Kenyan approach pairs political will and supply chain innovations with local action by health facility and community-based health workers to reach those most vulnerable to TB disease.

This presentation will demonstrate best practices and step-wise implementation guidance for replicating this success.

### **TPT Scale-Up in the Context of COVID-19: Early Experiences from Zambia**

P Lungu,<sup>1</sup> <sup>1</sup>National Tuberculosis Programme, Lusaka, Zambia. e-mail: lungupatrick99@gmail.com

Since 2017, Zambia has been scaling-up TPT among PLHIV, though challenges with supply chain stymied efforts. In 2018 and 2019, Zambia doubled the number of eligible PLHIV receiving TPT each year, though nearly 75% of eligible PLHIV had yet to complete TPT. In December 2019, the Ministry of Health set an ambitious goal of providing TPT to all PLHIV by the end of 2020. In February 2020, Zambia launched a campaign to rapidly scale-up TPT at high-volume facilities across the country, aiming to initiate 100,000 eligible PLHIV each month. Just as Phase One of TPT scale-up was underway and achieving early success, COVID-19 caused the MOH to abruptly shift course, adjusting screening protocols, scripting intervals, medication delivery, and the pace of its surge. This presentation will provide an overview of these challenges and early experiences with the strategies and approaches used to tailor the response in the midst of COVID-19.

### **Considerations for Implementing Effective TPT Programs**

A Kanchar,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: kanchara@who.int

Uptake of TPT among PLHIV has increased substantially in recent years, especially through the US President's Emergency Plan for AIDS Relief, which has prioritized TPT as part of routine and comprehensive care for all PLHIV. As part of planning, implementation and scale up of TPT among PLHIV, more focus and information are needed around how to assure effective and quality program implementation.

Important considerations for TPT programs include how to develop processes and systems to monitor potential adverse events associated with TPT, how to develop innovative approaches to support treatment ad-

herence and completion, how to engage communities and civil society in creating demand for these services, and how to approach and manage TPT among pregnant women.

This presentation will highlight a number of these key considerations to promote quality and effectiveness of TPT programmatic implementation and ensure its desired impact on reducing TB morbidity and mortality.

## **SYMPOSIA: SATURDAY 24 OCTOBER 2020**

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### **SP-41 Preventing human rights abuses in the digitisation of the TB and COVID-19 responses.**

#### **Big Data in the TB and COVID-19 Responses: A Neocolonial and Human Rights Analysis**

K Albrecht,<sup>1</sup> <sup>1</sup>Northwestern University, Evanston, United States. e-mail: kat.albrecht@nlaw.northwestern.edu

With the advent of big data comes increased potential for exacerbating disparity through data both directly and indirectly. The production of personal data in high TB burden countries, in particular, must be considered in light of their colonial histories.

Importantly, interventions intended eliminate TB at global and national levels are ushering in a new era of data commodification, colonization, and surveillance in the name of public health.

This, in turn, raises critical concerns for the human rights of people affected by TB, many of whom belong to vulnerable or marginalized groups. Importantly, examining the relationship between TB, data surveillance, and human rights law does more than illuminate potential pitfalls – it also foreshadows possible solutions.

#### **Watch Out for DAT Trojan Horse: DATs v. DOT for TB Treatment**

B Citro,<sup>1</sup> <sup>1</sup>Northwestern Pritzker School of Law, Chicago, United States. e-mail: citro@law.northwestern.edu

The proliferation of digital adherence technologies (DATs) in the TB response is thought to signal a departure from the longstanding approach of directly observed therapy (DOT). But are the two approaches really any different?

This talk will consider whether DATs, rather than representing a true break from DOT, are instead a Trojan Horse of sorts. That is, do DATs simply prolong the global community's reliance on an outdated treatment paradigm, while introducing a whole new set of concerns?

This question must be considered in light of the fact that DATs will generate massive amounts of personal data of people affected by TB—some of the most vulnerable people in our communities—for use by government and, in some cases, private health authorities.

### **The risks of digitization for surveillance and Contact Tracing for TB and COVID-19,**

M Laibuta,<sup>1</sup> <sup>1</sup>Kenyan School of Law, Nairobi, Kenya. e-mail: mugambi@laibuta.com

Apart from debate on Covid-19, conversations on privacy and data protection have gained momentum over the last few months. Questions have arisen on whether strategies to manage the Covid-19 have clawed back on gains made in protection of fundamental rights and freedoms especially the right to privacy.

Also, whether such strategies have been well thought out and whether they are proportion in view of their purpose. There is genuine concern that the surveillance mechanisms that have been adopted by states to deal with the pandemic have gone or will go beyond their legal purpose. Surveillance mechanisms have gradually moved from physical surveillance by health care professionals to surveillance by security agents and digital surveillance using mobile phone data.

Hence, there is need to interrogate what form of digital contact tracing would not pose unnecessary risks to the protection and promotion of fundamental rights and freedoms.

#### **Opportunities and Risks for Digital Technologies in TB Community-Led Monitoring**

C Smyth,<sup>1</sup> <sup>1</sup>Stop TB Partnership, Geneva, Switzerland. e-mail: caoimhes@stoptb.org

The reliance on comprehensive, high quality, and timely data and information on the barriers faced by people affected by TB in accessing essential TB services has given rise to the need for community-led monitoring (CLM) of the TB response and digital CLM solutions. Intended for collecting, exchanging and making accessible, data and information about the TB response as evidence for action, the ultimate aim of CLM is to close the gap in the number of people who fail to receive TB care. Ensuring rights and protections of populations engaged in its pursuit is an ethical and programmatic imperative. This talk will consider the opportunities for digital solutions in CLM, the ethical dilemmas that arise in CLM data-management and potential solutions.

## SP-42 Take home messages for active case finding learned from TB prevalence surveys, TB or not TB?

### The screening and diagnostic algorithm of national TB prevalence surveys: updated global guidance

C Sismanidis,<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: sismanidisc@who.int

Results from recent national TB prevalence surveys have been used to update the guidance from the WHO Global Task Force on TB impact measurement on the screening and diagnostic algorithm of these surveys. This presentation will be informing participants about the recent evidence, a chronology of the discussion and the new guidance.

### GeneXpert and Culture for all in the Mozambique national TB prevalence survey, ensuring quality of lab procedures and addressing discordant results

D Macheque,<sup>1</sup> <sup>1</sup>Ministry of Health, Mozambique/ National TB Control Program, Maputo, Mozambique. e-mail: david.macheque@hotmail.com

This presentation will address the key lessons learnt from doing culture and xpert for all participants in a nationwide survey in Mozambique. For all those with discordant field Gene Xpert and central lab culture result further laboratory testing was done amongst which subculture on MGIT. Experiences will be shared on the use of the GeneXpert MTB/RIF in the field setting, the performance of the culture including quality control measures for all sample transported to the National Tuberculosis Reference Laboratory as well as staff management.

It will highlight not only the importance of log tags for quality control of samples sent for culture and the use of controls (positive and negative) in the processing of samples in the NRTL, but also the impact of the survey results for TB control on the design of future strategies for TB testing in community settings.

### Strategies to minimize culture in TB prevalence surveys – lessons from targeted culture testing in the TREATS project

E Klinkenberg,<sup>1</sup> <sup>1</sup>Independent Consultant, the Hague, Netherlands. e-mail: evelineklinkenberg@gmail.com

TREATS measures the impact of the HPTN071 (PopART) intervention of combined universal HIV and TB screening and treatment on the burden of TB at population level.

Key to measurement is a TB prevalence survey conducted in 56,000 randomly sampled individuals from the tribal communities in Zambia and South Africa. To decide on the best algorithm for the study and contribute to global insights for national surveys, an “intensive diagnostic phase” was conducted to provide robust evidence on the optimal diagnostics algorithm for use in such TB prevalence surveys resulting in an innovative algorithm minimizing the use of culture.

Results will be presented outlining the evidence base behind this algorithm.

## SP-43 COVID-19 in pregnant women

### Pathogenesis and immunology of COVID-19 in pregnant women

K Waldorf,<sup>1</sup> <sup>1</sup>University of Washington, Seattle, United States. e-mail: adamsk@uw.edu

The Washington State COVID-19 in Pregnancy Collaborative was established to identify known pregnant COVID-19 cases from 16 major tertiary referral centers and community hospitals representing >40% of the ~86,000 annual deliveries in Washington State. In order to improve our understanding of how SARS-CoV-2, the virus that causes COVID-19 impacts the health of pregnant women and their newborns, a multi-pronged approach is needed including population based efforts to describe pregnancy outcomes among women with COVID-19, as well as detailed immunologic studies including placental innate immune responses to SARS-CoV-2.

We will discuss the pathogenesis and immunology of COVID-19 in pregnancy, including lessons learned from other emerging infectious diseases.

### Pregnancy and Postpartum Outcomes of COVID-19 in New York City: A Multi-center Prospective Cohort Study

M Prabhu,<sup>1</sup> <sup>1</sup>Weill Cornell Medicine, New York, United States. e-mail: map9403@med.cornell.edu

Over 700,000 confirmed cases of SARS-CoV-2 and 20,000 deaths from COVID-19 have occurred in New York City, making it the epicenter of the infection with fatalities topping that of many European countries. Early in the pandemic, pregnant women were noted to be asymptomatic carriers of SARS-CoV-2, and New York rapidly instated a universal screening program.

In this talk, the findings from this prospective cohort will be discussed, including maternal presentation, obstetric and neonatal outcomes, and placental pathology associ-

ated with COVID-19 infection. We will also discuss the evolution of maternal symptoms throughout the course of labor and the postpartum period, with implications for postpartum care.

### **Use of Remdesivir for Moderate to Severe COVID-19 in Pregnancy**

**M Das,**<sup>1</sup> <sup>1</sup>Gilead Sciences, Foster City, United States.  
e-mail: moupali.das@gilead.com

Remdesivir is one of the promising treatments being investigated for the treatment of COVID-19. Gilead, the manufacturer of Remdesivir, allowed compassionate use of Remdesivir for pregnant women with moderate to severe COVID-19.

In this talk, they will present the experience of 86 pregnant women who received compassionate-use Remdesivir, including baseline demographic and clinical characteristics, their time to recovery, and time to discharge. For women who delivered, birth outcomes and postpartum complications will be characterized. This data will be important groundwork for future clinical trials that include pregnant women.

### **Crowd-sourcing knowledge for COVID-19 in pregnancy with the WHO registry: Potential for maternal TB and beyond?**

**A Thorson,**<sup>1</sup> <sup>1</sup>World Health Organization, Geneva, Switzerland. e-mail: thorsona@who.int

To understand how SARS-CoV-2 infection during pregnancy impacts COVID and pregnancy and post-partum outcomes, the World Health Organization (WHO) has developed a standardized clinical registration platform with a specific module targeting pregnant women.

Further, a standardized research protocol has been designed. The protocol allows each site to adapt based on resource availability and local circumstances, and provides the option to focus on national analyses or participate in pooling. Knowledge of TB in pregnancy is still scarce.

This presentation will discuss possibilities to build on above experiences through different methods related to SARS-CoV-2, and possible implication to TB.

### **SP-44 Self-clearance of Mycobacterium tuberculosis infection: needs and consequences**

#### **Self-clearance and the denominator: who is still at risk and what does that mean?**

**R Houben,**<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
e-mail: rein.houben@lshtm.ac.uk

The presentation will provide definitions around self-clearance of Mtb infection and distal progression to disease, and summarise historical and current evidence for self-clearance. Using those observations, the consequences for the reservoir of viable Mtb infections will be discussed, both in likely overall size and distribution across countries and age groups.

Finally, the implications of this change in the denominator, i.e. the population at risk of distal progression, will be discussed.

#### **Self-clearance and the numerator: evidence for disease from distal Mtb infections**

**K Dale,**<sup>1</sup> <sup>1</sup>The Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.  
e-mail: katie.dale@mh.org.au

The presentation will evaluate the evidence for disease from a distal Mtb infection, which has been a source for debate in recent years. Empirical and modelling evidence will be considered.

#### **Testing for self-clearance: needs and progress**

**C Broderick,**<sup>1</sup> <sup>1</sup>Imperial College London, London, United Kingdom. e-mail: c.broderick@imperial.ac.uk

Our understanding of Mtb self-clearance is greatly limited by our current diagnostic tests, which cannot distinguish between those with ongoing viable Mtb infection, and those who have cleared it but remain immunologically sensitized to Mtb.

This presentation will consider the limitations of current tests for Mtb infection and discuss the need, potential applications and impact of a test of Mtb clearance. Novel approaches, including transcriptomics, for evaluating Mtb clearance will be presented.



## **TB vaccines and self-clearance: consequences for development and research**

R White,<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
e-mail: Richard.White@lshtm.ac.uk

If Mtb infection is not lifelong, this has consequences for how TB natural history of Mtb infection is conceptualised.

One immediate question is how self-clearance might affect natural protection against reinfection, and what this might mean for the potential impact of new TB vaccines. In this session I will discuss this issue, and what it might mean for TB vaccine development.

## **SP-45 Modelling to advance prevention**

### **Optimizing Investments in Mozambique's Tuberculosis Response**

P Zindoga,<sup>1</sup> <sup>1</sup>National TB Programme, Maputo, Mozambique. e-mail: pereirazindoga1@gmail.com

Mozambique is one of the 30 highest TB burden countries in the world. To achieve the goal of ending TB by 2035, it is crucial to determine which models of TB care and prevention should be prioritized. This is especially important in the context of limited resources, where options to prevent future TB cases may often be overlooked.

We used Optima TB, a mathematical model of TB transmission and disease progression, integrated with an economic and programme analysis framework, to consider different policy options.

We determined that Mozambique is not on track to meet the 2035 End-TB targets, and more funding for the TB program is required to reach strategic TB targets.

### **The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multi-drug resistant tuberculosis in China and India**

C Weerasuriya,<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
e-mail: c.weerasuriya@lshtm.ac.uk

Despite recent advances through the development pipeline, how novel TB vaccines might affect MDR-TB is unknown. We investigated the epidemiologic impact, cost-effectiveness and budget impact of hypothetical novel prophylactic prevention of disease TB vaccines on MDR-TB in China and India.

We constructed a dynamic model of TB, introducing novel vaccines from 2027 with post- (PSI) or both pre- and post- infection (P&PI) effectiveness, conferring 10 years of protection, with 50% efficacy. By 2050, the P&PI vaccine reduced RR/MDR-TB incidence rate by 70% and 68%, and the PSI vaccine by 29% and 38% in China and India.

Our model predicted that a US\$10 P&PI vaccine would be cost-effective at the GDP and healthcare opportunity cost threshold, and PSI vaccine cost-effective at the GDP threshold, in both China and India. TB vaccination will likely contribute to MDR-TB control, and may be cost-effective but depends on vaccine characteristics and setting.

### **Risk-benefit analysis of tuberculosis infection testing for household contact management in high-burden countries**

C Yuen,<sup>1</sup> <sup>1</sup>Harvard Medical School, Cambridge, United States. e-mail: courtney\_yuen@hms.harvard.edu

High-tuberculosis-burden countries expanding preventive therapy (PT) use must decide how tuberculosis infection testing should be used for risk stratification among household contacts of tuberculosis patients.

We modelled the risk of tuberculosis disease and risk of severe adverse events, comparing two PT strategies: PT for all household contacts, or PT for only household contacts with a positive tuberculin skin test. We used data from clinical trials and literature on tuberculosis natural history to model outcomes assuming different PT regimens, ages, and tuberculin skin test positivity prevalences.

Our findings suggest that in high-burden settings giving PT to all contacts <18 years old would lead to substantially more protection with minimal additional adverse events compared to giving PT to only those with confirmed infection. For older contacts, adverse events are more of a concern; these can be minimized by using a rifampicin-only regimen and focusing PT on those with a positive infection test.

### **Cost-effectiveness of interventions to scale up short course TB preventive therapy among children, in 12 countries**

Y Jo,<sup>1</sup> <sup>1</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, United States. e-mail: youngji1435@gmail.com

We assessed the cost-effectiveness of household contact investigation for children under 5 years old across 12 high TB burden countries. We compared three scenarios:

- (a) status quo,
- (b) contact investigation with treatment of active TB only, and
- (c) contact investigation with treatment of active TB and provision of short-course preventive therapy (3HP) for latent TB infection.

We used data from the literature and a large 12-country implementation study to estimate country-specific incremental cost-effectiveness ratios. We projected that contact investigation with treatment of active TB and provision of preventive therapy is highly cost-effective compared to TB treatment only (\$111 per disability-adjusted life year [DALY] averted) or status quo (\$353 per DALY averted).

Key drivers of cost-effectiveness were TB prevalence among contacts and case fatality of untreated TB. Screening child contacts for active TB and provision of short-course treatment for latent TB infection can be cost-effective in high burden settings.

### **Modelling to advance prevention: a patient advocate's perspective**

A von Delft,<sup>1</sup> <sup>1</sup>Centre for Infectious Disease Epidemiology and Research, University of Cape Town & TB Proof, Cape Town, South Africa. e-mail: vuzumsi@gmail.com

COVID-19 has wrenched the world's attention back to the importance and value of infectious disease modelling. In South Africa such models were crucial in informing what has been hailed by the WHO as a world-leading preventive approach to this pandemic.

As a Public Health doctor and activist I have been delighted, but as a TB activist living with latent MDR-TB the contrast could not be more stark. TB remains the leading cause of death in SA, yet our approach has been focused far too much on reactive treatment, with a lack of evidence frequently cited as an excuse for token investments in prevention. Health workers were already dying from TB contagion in unacceptable numbers long before SARS-CoV-2 reminded us what happens if we fail to care for our carers. Modelling can help with these complex challenges – we must never again allow any infectious diseases to spread unchecked among us.

### **SP-46 Subclinical TB disease: lessons and questions from field to lab**

#### **Subclinical TB disease: What do we know, what do we need to know**

H Esmail,<sup>1</sup> <sup>1</sup>University College London, London, United Kingdom. e-mail: h.esmail@ucl.ac.uk

It is becoming clear that a two state latent active paradigm is overly simplistic and limits approaches to TB control.

In this talk data will be presented from both a historical systematic review and a contemporary study to provide fresh insight into the subclinical disease state and

the heterogeneous kinetics of disease progression. The implication of this for diagnostic and intervention strategies will then be explored.

### **Lessons from the field: experiences from a mass X-ray screening programme**

N V Stavitskaya,<sup>1</sup> <sup>1</sup>Novosibirsk Tuberculosis Research Institute, Novosibirsk, Russian Federation. e-mail: stavitskaya@mail.ru

One approach to address subclinical TB for a TB care and prevention programme is to employ mass-Xray screening. Until recently, this approach has been employed in a number of countries. Rather than re-invent the wheel, there are valuable insights for countries considering this policy option.

This presentation will outline the benefits, costs and political background of the mass-Xray screening in Russia.

### **Lessons from the lab: what is the biological basis for subclinical TB?**

T Scriba,<sup>1</sup> <sup>1</sup>University of Cape Town, Cape Town, South Africa. e-mail: Thomas.Scriba@uct.ac.za

Blood-based transcriptional diagnostics have been proposed as tests that may be able to identify those with culture positive prevalent disease and potentially also predict those who will develop disease in subsequent months.

This presentation will highlight insights into this from the recently completed CORTIS trial and discuss the strengths and limitations of this approach as a future tool in the active case finding context and insights into the host response during subclinical phase of disease.

### **Lessons from the breath: better predictor of transmission or disease?**

C Williams,<sup>1</sup> <sup>1</sup>University of Leicester, Leicester, United Kingdom. e-mail: cw329@leicester.ac.uk

TB is transmitted by aerosolization of Mtb. Traditionally we have relied upon spontaneous sputum production as the primary sample for case detection and a proxy for infectiousness. While cough is usually considered the primary driver of aerosolization facilitating transmission, this dogma is now being challenged, especially in the context of subclinical disease.

This presentation will build on recent insights using face masks to capture aerosols in community screening, active case finding and transmission studies, and explore the impact of these findings on the current paradigms around Mtb transmission and what this might mean for testing for clinical and subclinical disease.

## Lessons from the population: how infectious is subclinical TB?

J Emery,<sup>1</sup> <sup>1</sup>London School of Hygiene and Tropical Medicine, London, United Kingdom.  
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One of the key questions around subclinical TB remains the contribution to transmission from this asymptomatic, bacteriologically-confirmed population. If cough is absent or limited, how effective is transmission, and how do other aspects of subclinical disease affect transmission? To address these questions, the presentation will bring together empirical data on the relative infectiousness of subclinical TB. Through a simple model, the presentation will provide an estimate of the proportion of all population transmission that is due to subclinical TB in Viet Nam, a high burden country with a substantial burden of subclinical TB.

## SP-47 Youth mobilisation to boost the fight to End TB

### Mobilizing young people as powerful advocates to end TB

M Kaphle,<sup>1</sup> <sup>1</sup>WHO, Kathmandu, Nepal.  
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Despite being the world's top infectious killer, awareness about TB is poor, especially among young people who are among those most affected. Information campaigns, peer education and community mobilization through social media and in-person are some ways that Madhusudan has reached thousands of young people.

In this presentation he talks about what he has learnt about educating, mobilizing and motivating young people to become leading voices in the fight to end TB. He also presents the results of the online consultation, which take these learnings and apply them to new and innovative approaches at reaching young people.

### Making solidarity infectious: how young people can fight stigma and discrimination against people with TB

P Sarimita Winarni,<sup>1</sup> <sup>1</sup>Youth Movement Against TB in Indonesia, DKI Jakarta, Indonesia.  
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People with TB face immense stigma and discrimination that can hamper their access to care, as well as their psychosocial wellbeing. While young people are traditionally social justice champions, what role can they play in raising awareness and fighting stigma for TB

patients? Paran looks at this from her personal experience as TB survivor and advocate, as well as experiences collected from around the world and through the online consultation.

### Not just diagnostics and medicines: how young people can support those with TB through treatment and recovery

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People with TB face a challenging recovery period and need psychosocial and socioeconomic support to complete their treatment and lead fulfilling lives after surviving the disease. How can young people contribute to this? Funke Dosumu, a TB survivor and advocate, looks at the role each young person can play in supporting TB patients, including using new digital tools to respond better to this need.

### Boosting research and innovation to end TB: young people have a role to play

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Despite being an old and deadly infectious disease, there is still no point of care test, few new drugs, and no effective preventive vaccine against TB. Phumeza Tisile, who lost her hearing as a side-effect of treatment of drug-resistant TB, has a lot to say about the importance of innovation. Here she talks about how young people can provide society an impetus to invest in research and development – both by individual contributions and by shaping society's priorities.

### Getting invested: young people's role in bringing all of society on board and increasing funding to end TB

H Nguyen,<sup>1</sup> <sup>1</sup>Vietnam Integrated Center for TB and Respiratory Research/National TB Control Program, Hanoi, Vietnam. e-mail: nguyenviethai.hmu@gmail.com

How do you bring society to take ownership of its TB response – addressing not only the healthcare aspects, but the social determinants of the disease? Along with the Ministry of Health, how do we include other ministries such as for disabilities, for women and child health, for education, for labour, for finance in the response? How do we involve local governments, mobilize the private sector, and activate civil society?

Hai will speak about an all-of-society approach to ending TB, building on experience from Viet Nam, as well as an international stage and the online consultation.

### **SP-48 Understanding the impact of participatory approaches in developing sustainable TB policies**

#### **The role of national dialogues in ensuring policy sustainability – best practices and lessons learned**

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Using the TB Europe Coalition's extensive experience facilitating national dialogues for participation in policy-making, Mariya Makovetska will present the best practices that have been developed in this area to bridge the gap between civil society organizations and the health services to provide people-centred TB services and lessons learned, for other organisations and regions to use and adapt.

#### **Barriers to participatory approaches to policymaking**

P Sommerfeld,<sup>1</sup> TB Europe Coalition, London, United Kingdom. e-mail: paul\_sommerfeld@tbcoalition.eu

While there is increasing recognition of the importance of participatory approaches, this is by no means universal.

In this presentation, Paul Sommerfeld will highlight some of the main barriers that TBEC has faced in its work in this regard over the past decade. He will also explore some of the paths he has taken to overcome obstacles and ensure the successful inclusion of civil society groups in policy change. This provides an opportunity for other groups to learn and develop their own strategies.

#### **Civil society on the road to a TB law**

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In November 2018, Romania adopted a Law for TB Prevention and Control. This includes sick leave entitlement throughout treatment and ambulatory nutritional support. The process of ensuring the law's adoption was a long process, taking years of consolidated work from civil society.

In this presentation, Cristina will explore the ways that civil society groups and individuals worked to ensure the law's adoption over this period, providing lessons for other countries, as well as demonstrating the vital role of individual and organisational participation in policy development.

### **Participatory approaches in action: collaboration between WHO and civil society to end TB**

Y Chorna,<sup>1</sup> TB Europe Coalition, Kiev, Ukraine.  
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The panel presentation will reflect on the collaboration between WHO and civil society within the aspects of the participatory approaches, including WHO ENGAGE-TB framework. This can be seen in the establishment of the WHO Civil Society Task Force on TB and the RCC-THV. Throughout the last few years, the participation of civil society and TB affected communities in NTP reviews has been facilitated through the support of the WHO Regional Office for Europe. This engagement allowed for grassroots perspectives as to the success and barriers in TB programmes to be voiced, as well as providing recommendations for the format of quality people-centered care based on the personal experience of former patients.

Presentation will raise awareness of the interested stakeholders on the opportunities for participatory approaches to end TB as well as further areas of strengthening intersectorial collaboration.

## ABSTRACT PRESENTATIONS WEDNESDAY 21 OCTOBER 2020

### ORAL ABSTRACT SESSION (OA)

#### OA-01 TB preventive therapy in HIV

##### OA-01-500-21 Isoniazid preventive therapy (IPT) interruptions and tuberculosis (TB) among people living with HIV (PLHIV) in the Democratic Republic of the Congo (DRC)

I. Thior,<sup>1</sup> A. Nkulu,<sup>2</sup> V. Cikobe,<sup>2</sup> C. Banzakadilo,<sup>2</sup> J. Zaki,<sup>1</sup> D. Canagasabay,<sup>1</sup> P. Milenge,<sup>2</sup> J.-C. Kiluba,<sup>2</sup>  
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**Background and challenges to implementation:** DRC has the third highest TB burden in Africa (incidence: 321 cases/100,000 persons) and an HIV prevalence of 1.2% among the general population. IPT (nine-month regimen per national guidelines) is an important prevention intervention for PLHIV, but INH shortages and IPT interruptions have been frequently reported in DRC.

**Intervention or response:** PATH, through the USAID-funded IHAP-HK project, analyzed programmatic data to assess the occurrence of TB cases among PLHIV on IPT and understand the potential impact of INH interruptions on IHAP-HK's PLHIV cohort, using patient-level data extracted from Tier.Net.

We analyzed TB cases among PLHIV enrolled in IPT in Haut Katanga Province, using descriptive statistics to describe basic variables, nonparametric t-test to compare medians, and a multivariate analysis to identify significant predictors of TB.

**Results/Impact:** From March 2010 to August 2019, 12,299 PLHIV initiated IPT, of whom 68% were female. Males were older (34 years; interquartile range [IQR]: 22-43) at IPT initiation than females (32 years; IQR: 25-39). 140 TB cases were diagnosed, with similar prevalence among males (1.1%) and females (1.2%).

Of those who completed IPT, only 0.4% developed TB compared to 4% among those with interrupted IPT. IPT (adjusted OR [aOR]=0.081—95% CI [0.034–0.18]) and age group (>30 to 37 years; aOR=6.2—95% CI [2.75–14]) were independent predictors of TB after controlling for sex, World Health Organization (WHO) staging at IPT initiation, and age at IPT initiation. PLHIV who did not complete IPT were 12 times more likely to be diagnosed with TB than those who completed IPT.

**Conclusions:** This analysis reinforces the importance of IPT adherence to prevent TB among PLHIV and the critical need for a reliable INH supply. To mitigate the impact of INH shortages, IHAP-HK is now prioritizing INH for PLHIV already on IPT and reducing IPT duration to six months, in alignment with WHO recommendations.

##### OA-01-501-21 The effect of antenatal isoniazid preventive therapy on birth outcomes in Western Kenya

E. Quincer,<sup>1,2</sup> A. Lyland,<sup>3,4</sup> D. Onyango,<sup>5</sup> J. Figueroa,<sup>2</sup> A. Odhiambo,<sup>5</sup> S. LaCourse,<sup>6,7</sup> G. John-Stewart,<sup>6,7,8,9</sup> L. Cranmer,<sup>1,2</sup>  
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**Background:** Tuberculosis (TB) in pregnancy results in poor maternal and infant outcomes. Pregnant women living with HIV are at high risk for TB, yet there is conflicting evidence on the safety of antenatal isoniazid preventive therapy (IPT). We evaluated the effect of IPT on birth outcomes in a programmatic setting.

**Design/Methods:** We completed a retrospective chart review of antenatal and birth records of mother-infant dyads at two health care facilities in Kisumu, Kenya from 2015 – 2020. Among pregnant women >18 years with data on IPT use, ART and viral load, we assessed the relationship of antenatal IPT exposure with birth outcomes (preterm delivery, low birth weight, congenital anomalies, and perinatal death) using Chi-squared or Fisher's Exact tests and multivariable logistic regression.

**Results:** Of 779 medical records screened, 576 mother-infant pairs had complete data. Median maternal age was 29 years (IQR 26-33) and most women were on ART [574 (99%)] with viral suppression <1,000 copies/mL [555 (97%)]. About one-third of women used IPT during pregnancy [156 (27%)]; median gestational age at IPT initiation was 23 weeks (IQR 11-43). The prevalence of preterm birth was lower among women with antenatal IPT (21% vs. 30%, p = 0.03). Low birth weight, congenital anomaly and perinatal death were not associated with antenatal IPT, though we observed a trend of lower composite poor birth outcomes among women taking

antenatal IPT (26% vs. 33%,  $p = 0.08$ ). Controlling for maternal age, viral load and ART, the odds of preterm birth was lower among women who initiated IPT during pregnancy [aOR: 0.63 (95% CI 0.40, 0.98)].

**Conclusions:** Antenatal IPT use in women living with HIV was associated with lower rates of pre-term birth in a programmatic setting. Our data add evidence that IPT can be safely used in pregnancy and provide benefit to HIV-infected women and their infants.

### OA-01-502-21 Birth outcomes of pregnant women exposed to isoniazid preventive therapy

S. Masuku,<sup>1</sup> T.B. Sole,<sup>1</sup> M. Van Der Walt,<sup>1</sup> T. Reddy,<sup>2</sup> K. Motlhaleng,<sup>3</sup> M. Cheyip<sup>3</sup>. <sup>1</sup>South African Medical Research Council, Tuberculosis Platform, Pretoria, South Africa, <sup>2</sup>South African Medical Research Council, Biostatistics Unit, Durban, South Africa, <sup>3</sup>Centers for Disease Control and Prevention, Care and Prevention, Pretoria, South Africa.  
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**Background:** Background: Tuberculosis (TB) is associated with increased risk of death and morbidity among pregnant women, particularly those living with human immunodeficiency virus (HIV). Both pregnancy and HIV increase the risk of TB disease. Antiretroviral therapy and isoniazid preventive therapy (IPT) can reduce mortality rates among HIV-positive pregnant women in high-burden settings. We assessed initiation of IPT and birth outcomes among eligible HIV-positive pregnant women.

**Design/Methods:** Design/Methods: We analyzed data from 1,215 HIV-positive consenting pregnant women in their second or third trimester; participants were prospectively enrolled from six facilities across three provinces (Gauteng, KwaZulu-Natal, and Mpumalanga) in South Africa (October 2017–May 2019). IPT exposure and non-exposure were calculated according to South Africa's guidelines. We ran a multinomial logistic regression to assess the association between IPT exposure and pregnancy outcomes, with standard errors of parameters adjusted for clustering by facility. All analysis was conducted using Stata 15 and p-values less than 0.05 were considered statistically significant.

**Results:** Results: Of the 1,215 HIV-positive pregnant women, 833 (68.6%) reported IPT initiation during pregnancy, of which 786 had known pregnancy outcomes. Of women who were not receiving IPT, <20% reported history of IPT exposure. Over 90% of live births were recorded among the enrolled women. Women receiving IPT were significantly more likely to experience live birth outcomes (94.9%) than IPT-unexposed women (92.6%;  $p=0.017$ ) and were less likely to have a miscarriage and a still birth.

**Conclusions:** Conclusion: IPT exposure during pregnancy yielded significantly higher live birth rates and were less likely to have miscarriage and still birth. These

findings suggest that IPT can be safely used during the second and third trimester of pregnancy. With recent changes in TB and HIV treatment regimens, more research is needed to determine the safety of these therapies during each trimester of pregnancy and to evaluate pregnancy outcomes.

### OA-01-503-21 Isoniazid preventive therapy added to ART to prevent TB disease: an individual participant data meta-analysis

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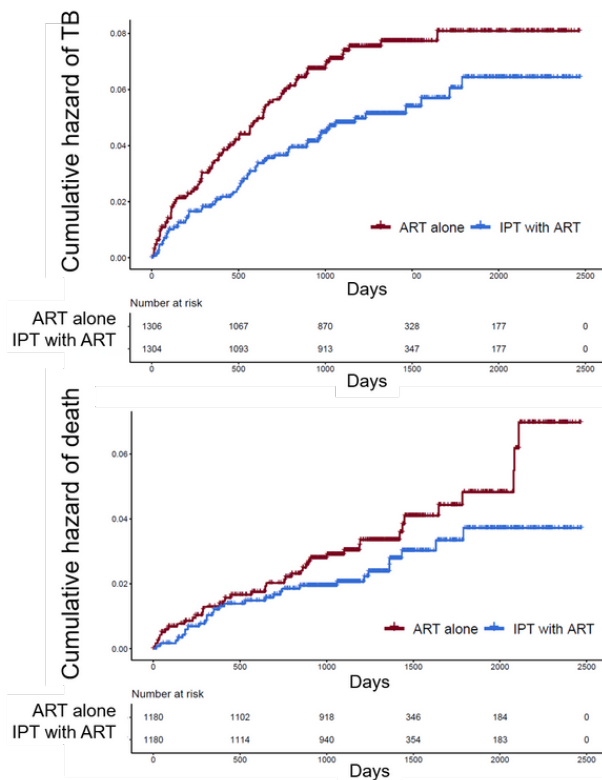
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**Background:** Isoniazid preventive therapy (IPT) prevents TB in people living with HIV (PLHIV). We conducted an individual participant data meta-analysis of randomized controlled trials to estimate the effect of IPT given with antiretroviral therapy (ART) to prevent TB and death among PLHIV across subgroups by sex, baseline CD4 cell count, and immune sensitization to TB.

**Design/Methods:** We searched PubMed, Embase, and the Cochrane database for studies published through January 2019 and conference abstracts. Eligible studies included trials of HIV-positive adults taking ART, randomized to daily IPT versus no IPT, and longitudinal follow-up for incident TB and death. We performed a single-stage individual participant data meta-analysis of the outcomes of incident TB disease and all-cause mortality using stratified Cox-proportional hazards models. The study protocol was registered with PROSPERO (CRD42019121400).

**Results:** We found 838 unique citations and included three trials with participants in Cote D'Ivoire, Malawi, and South Africa, 2611 participants for the TB outcome and 2362 participants for the all-cause mortality outcome. IPT with ART was associated with lower risk for

TB than ART alone (hazard ratio=0.69, 95% CI 0.50–0.96,  $p=0.03$ ) and a trend towards lower all-cause mortality (hazard ratio=0.69, 95% CI 0.43–1.10,  $p=0.12$ ). TB risk differed by baseline CD4 <200 cells/mm<sup>3</sup>, but there was no evidence of varying benefit of IPT with ART by sex, baseline CD4, or results of tuberculin skin test (TST) or interferon gamma release assays. Grade 3-4 liver injury occurred in 22/1307 (1.7%) participants taking ART versus 43/1304 (3.3%) taking IPT with ART, including 12/124 (9.7%) participants additionally taking daily fluconazole.



**Conclusions:** IPT given with ART prevents TB across demographic and HIV- and TB-specific subgroups, including among PLHIV without evidence of immune sensitization to TB. This contrasts with earlier trials of IPT without ART that found no benefit among PLHIV with a negative or unknown TST.

### OA-01-504-21 Impact of tuberculosis preventive therapy on tuberculosis incidence among persons living with HIV receiving antiretroviral therapy in Nairobi, Kenya (2015–2019)

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**Background:** Persons living with HIV (PLHIV) in Kenya have high tuberculosis (TB) comorbidity and mortality rates. To mitigate the TB burden, Kenya has provided TB preventive therapy (TPT) to all eligible PLHIV since 2012. PLHIV are screened for TB at every clinic visit; those without active TB initiate TPT (6-month daily isoniazid). By September 2019, over 85% of PLHIV receiving anti-retroviral therapy (ART) had initiated TPT. We describe TPT initiation and impact on TB incidence among PLHIV receiving ART at 14 Nairobi Faith-based clinics.

**Design/Methods:** We analyzed aggregated routine program data on TPT initiation and TB diagnosis among PLHIV receiving ART (October 2014–September 2019). For each 12-month reporting period (October–September), we used Epi Info (CDC, Atlanta, GA) to calculate TB incidence and the relative risk (RR) of TB among those who completed and those who never completed a course of TPT. P-values <0.05 were considered statistically significant. Data were reported quarterly to the US Centers for Disease Control.

**Results:** During the five reporting periods, 2,207 PLHIV receiving ART had a new TB diagnosis, including 565 who had completed TPT and 1,642 who never completed TPT. Overall TB incidence by year ranged from 2.5% (2015) to 1.4% (2019). For PLHIV who completed TPT, TB incidence was 0.7% on average (range, 0.4% in 2015 to 1.6% in 2019; trend test,  $p<0.001$ ). For PLHIV who never received TPT, TB incidence averaged 14.2% (range, 22.6% in 2015 to 6.8% in 2019). TB incidence was significantly lower among PLHIV who received TPT by age, sex and reporting periods. RR of having TB ranged from 0.016 (95% confidence interval[CI]: 0.013–0.020) in 2015 to 0.228 (95% CI: 0.195–0.267) in 2019 (figure).

**Conclusions:** We found that TPT scale-up among PLHIV in Nairobi substantially reduced TB burden; extending TPT coverage to all PLHIV globally could improve patient outcomes.

### OA-01-505-21 Comparing IsoScreen results and self-reported isoniazid preventative therapy adherence among HIV-positive pregnant women in South Africa

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**Background:** According to the South African guidelines on isoniazid preventative therapy (IPT) and pregnancy, IPT can be started anytime during pregnancy/breast-feeding provided that the woman is on lifelong antiretroviral therapy. In South Africa, IPT has been routinely offered since 2010 for it provides protection against TB. Assessing IPT adherence among pregnant women living with HIV (PWLHIV) was important given the country's investment into the therapy. We compared IsoScreen results and self-reported IPT adherence among eligible HIV-positive pregnant women.

**Design/Methods:** Pregnant women were purposely selected from six facilities of three provinces in South Africa (October 2017–May 2019). Project staff were permanently stationed at selected antenatal care facilities during data collection. HIV information was collected from participants' medical records, and IPT initiation was self-reported. Eligible HIV-positive pregnant women who provided a written informed consent received urine IsoScreen testing at any follow-up visit. The sensitivity of any positive result from the IsoScreen to detect isoniazid metabolites in the urine has been estimated to be 95%–99% at 24 hours and 85% at 48 hours after the last dose of 300 mg of isoniazid. An exact McNemar test was used to analyze the difference between IsoScreen results and self-reported IPT adherence; P-values <0.05 were considered statistically significant.

**Results:** Of 3,822 participants, 1,215 (31.8%) were HIV positive, and 833/1,215 (68.6%) were eligible and initiated IPT after enrolment. IPT adherence was significantly higher according to patients' self-reports (93.1%, 92.5%, and 96.0% at the first, second, and third visits, respectively) than to IsoScreen test results (51.5%, 51.6%, and 56.9%, respectively;  $p < 0.001$ ).

**Conclusions:** Our findings suggest that self-reporting for IPT adherence is prone to reporting bias and that IsoScreen is a reliable measure of adherence. Policy makers could consider integrating the IsoScreen test in routine programs to measure IPT adherence or treatment for active TB.

### OA-01-506-21 Suboptimal adherence to isoniazid preventative therapy using urine biomarker assessment in children living with HIV: association with viral suppression and age

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**Background:** Children living with HIV (CLHIV) are at risk for TB. Isoniazid (INH) preventative therapy (IPT) reduces a child's risk of TB by 60% but efficacy requires adherence. Data are limited on biomarker-confirmed IPT adherence in CLHIV. We present preliminary results of an ongoing study in western Kenya, which assessed IPT adherence using urine biomarkers.

**Design/Methods:** In this prospective cohort of CLHIV on programmatic IPT, adherence was assessed by caregiver- or child-report, pill counts, and urine biomarker testing using a low cost dipstick test monthly, and a commercial test (Isoscreen™) every 2-months. Both tests produce a characteristic color change in the presence of INH metabolites typically within 24–48 hours of ingestion. CLHIV with positive on either test at all time-points assessed were considered adherent. We evaluated risk factors of non-adherence using general linear modeling and calculated sensitivity and specificity of self-reports/pill counts with the dipstick test as a gold standard.

**Results:** Among 100 CLHIV, 54% (n=54) were male; median age was 10 years (IQR = 6–13). At IPT initiation 96% (n=96) were on ART for a median duration of 4 years (IQR=1–7); 83% (n=64/77) of CLHIV with programmatic viral load data were suppressed (viral load <500 copies/ml). Of 91 CLHIV with 251 urine tests, 81% (n=74) reported their last dose was within 48 hours, while 55% (n=50) had consistent biomarker-confirmed adherence. Biomarker-confirmed non-adherence was higher in virally unsuppressed than suppressed (RR=1.76; CI 1.08–2.88) and CLHIV aged under-five years than 5 to 14 years (RR=2.05; CI 1.39–3.02). The sensitivity and specificity of self-reported/pill count adherence was 93% (95% CI 89–98%) and 35% (95% CI 27–44%), respectively.

**Conclusions:** Adherence to IPT in CLHIV in western Kenya is sub-optimal particularly in virally unsuppressed and under-fives. Urine biomarkers may improve real-time adherence counseling in clinical settings.



## OA-02 Finding a needle in the haystack: where are children with TB?

### OA-02-507-21 Barriers to contact investigation among children: experience from Lagos, Nigeria

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**Background:** Case-finding among children has remained a daunting challenge in Nigeria. Case Notification among children has been consistently below 10% of the total cases in spite of the huge investments made on active case-finding. Several factors have been identified as contributors to this programmatic issue, aside from the difficulty in diagnosing TB among this group, they include social, economic, cultural and religious factors. This is further compounded by the difficulty in conducting contact investigation of children who are social and household contacts of index patients. It is crucial to understand the operational challenges as described by the health workers who are in contact with TB patients on a day to day basis.

**Design/Methods:** This study employed a qualitative approach using in-depth interviews. Key informant interviews of eight (8) health workers were conducted in Lagos State, Nigeria.

**Results:** Respondents identified stigma as a key barrier to case-finding among children. Contact tracing of adult index cases is complicated by several issues including wrong contact information given by patients, reluctance to disclose under-5 social and household contacts and failure to inform or bring such contacts to the hospital for TB investigation. All of these behaviors were linked to stigma by the health workers interviewed. Finance-related issues were also identified as a key barrier. One of the respondents stated that "I do not have money to visit them in their house and the patient cannot pay to bring their children to the hospital because they are not sick". Explaining the TB preventive therapy to patients was described as challenging by all health workers interviewed. Other challenges identified include difficulty in getting specimens from children.

**Conclusions:** The findings of this study suggest the need, for more investments towards addressing TB-related stigma in the general population, and the provision of financial support for health workers to conduct contact investigation.

### OA-02-508-21 Low-level care facilities as entry points for pediatric TB screening and case finding: a stepped-wedge randomized controlled study

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**Background:** TB remains a growing public health problem globally, and a major cause of under-five morbidity and mortality. Young children have historically been excluded from the global health focus of reducing transmission through early case finding and effective treatment.

This analysis aims to evaluate TB screening at different levels of care, in hubs (sub-county and county referral hospitals) and spokes (health centers and dispensaries that refer TB samples to hubs for processing).

**Design/Methods:** Using a stepped-wedge randomized controlled study design, we screened and enrolled children under 5 years, with presumptive TB, at different entry points in 32 study facilities (14 in Kenya and 18 in Cameroon) between May 2019 and March 2020. We describe the yield by entry points and facility type and used Pearson's chi-square to test for associations.

**Results:** There were 770 children screened with potential TB symptoms at facility entry points, 646/770 (84%) at hubs, and 124/770 (16%) at spokes; 364/770 (47%) were reassessed for signs and symptoms, while 406/770 (53%) received antibiotics for reassessment later. Of those reassessed, 275/364 (76%) were confirmed as TB presumptive. The proportion of children who were reassessed and were still TB presumptive was higher at spokes (59/70, 84%) than at hubs (216/294, 73%),  $P=0.058$ . Among presumptive TB cases, 208/275 (76%) children had TB investigations completed, 41/59 (69%) in the spokes, and 167/216 (77%) in the hubs,  $P=0.215$ . Finally, the proportion of confirmed TB diagnosis out of the overall number of initially screened with presumptive TB symptoms was higher in the spokes (23/124, 19%) than in the hubs (71/646, 10%),  $P=0.004$ .

**Conclusions:** Although the majority of children with presumptive and confirmed TB came from the hubs, the proportion of confirmed TB cases was higher in the spokes, suggesting the utility of decentralized active case finding in the lower-level care facilities.

## OA-02-509-21 A simple clinical score for predicting active tuberculosis when same-day microbiological testing is unavailable

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**Background:** In clinics that lack same-day microbiological testing for active tuberculosis (TB), a simple clinical risk score for predicting active TB could be useful.

**Design/Methods:** We analyzed data from adults tested for TB with Xpert MTB/RIF across 28 primary health clinics in rural South Africa. We used least absolute shrinkage and selection operator regression to identify characteristics associated with Xpert-confirmed TB and converted coefficients into a simple clinical score. We assessed discrimination using receiver operating characteristic curves, calibration using Cox's linear-logistic regression, and clinical utility using decision curves.

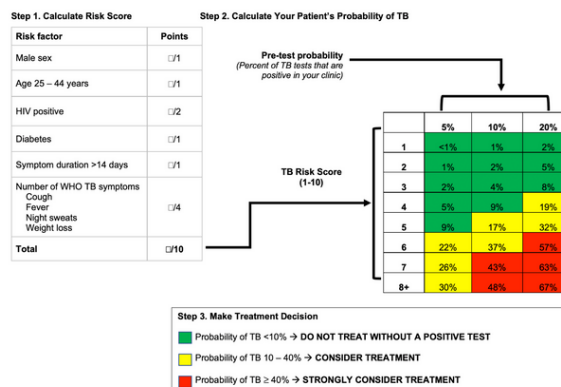
We validated the score externally in a population of adults tested for TB across four primary health clinics in urban Kampala, Uganda. The model development was repeated de novo with the Ugandan population to compare clinical scores.

**Results:** The South African cohort included 707 individuals who tested positive for TB and 702 randomly-selected individuals who tested negative. The final prediction model included six characteristics and a maximum 10 points [age 25-44 years, male sex, HIV (2 points), diabetes, classical TB symptoms (cough, fever, weight loss, night sweats – 1 point each), and >14-day symptom duration].

The model was validated in the Ugandan cohort of 106 Xpert-positive and 281 Xpert-negative adults. Discrimination was moderate in the derivation ( $c$ -statistic=0.82, 95%CI=0.81-0.82) and external validation ( $c$ -statistic=0.75, 95%CI=0.69-0.80) populations.

Optimal cut-offs for clinical use were a score of four (sensitivity=0.85, specificity=0.63) or five (sensitivity=0.69, specificity=0.80). A patient with 10% pre-test probability of TB would have a post-test probability of 4% with a score of three versus 43% with a score of seven. A model constructed de novo in the Ugandan population contained similar characteristics and performed equally well.

**Conclusions:** This simple clinical risk score can inform evidence-based empiric treatment decisions for TB in settings with constrained diagnostic resources where concern for pre-treatment loss to follow-up is high.



[Figure 1. A simple clinical risk score for empiric diagnosis of active tuberculosis - Shown is a one-page, easy-to-use tool for use in clinical settings where same-day microbiological testing for pulmonary tuberculosis is unavailable and risk of loss to follow-up is high. For illustrative purposes, we have chosen cutoffs of 10% and 40% risk of TB as potential clinical decision points, based on natural breaks in predictive probability and on intuition that TB treatment is unlikely to be started empirically for patients with less than a 1 in 10 chance of having TB. Other cutoffs could be selected based on local resources and probabilities of loss to follow-up if untreated.]

## OA-02-510-21 Key clinical features among children under five with a presumptive diagnosis of TB and confirmed TB diagnosis in sub-Saharan Africa

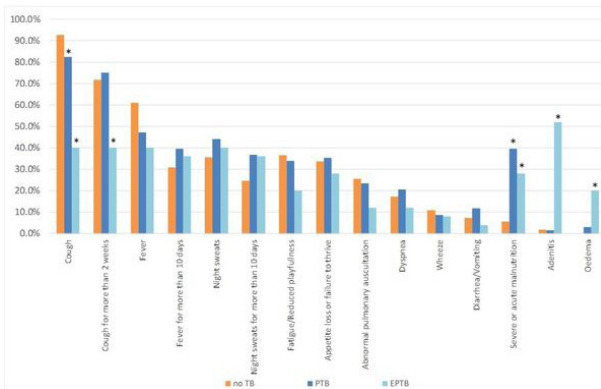
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**Background:** Children under the age of five years are at a high risk of developing and dying of active TB disease. Clinical symptoms in young children are less typical than adults and have been poorly described. We described the clinical presentation of under-five children with presumptive TB disease and with a confirmed TB diagnosis.

**Design/Methods:** We are conducting a stepped-wedge randomized controlled trial assessing interventions to improve pediatric TB case detection in Kenya and Cameroon. Under-five children, with parental written consent and symptoms screened as TB presumptive, are followed through TB diagnosis. We evaluate which clinical symptoms among children with presumptive TB are associated with a diagnosis of pulmonary (PTB) and/or extra-pulmonary TB (EPTB) using the Fisher exact test.

**Results:** Between May 2019 to March 2020, 203 children with presumptive TB completed diagnostic investigations, and 93/203 (46%) were confirmed with TB, 68/93 (73%) with PTB, and 25/93 (27%) with EPTB. Most children (82/93, 88%) were diagnosed based on a clinical-radiological algorithm, with 45/93 (48%) having a chest X-ray suggestive of TB. Although they were the most common symptoms in TB presumptive and diagnosed children, cough and fever were not associated with having a TB diagnosis confirmed.

Adenitis and edema were rare symptoms overall but were more frequent in children later confirmed with EPTB (adenitis: 13/25 (52%) versus 2/110 (2%), edema: 5/25 (20%) versus 0/110,  $P < 0.001$ ). Most EPTB children with edema (4/5, 80%) and 6/13 (46%) of those with adenitis did not have associated fever or cough. Severe or moderate acute malnutrition was much more frequent in children with confirmed TB diagnosis (34/93, 37%) than non-TB cases (6/110, 5%),  $P < 0.001$ .



[Figure]

**Conclusions:** In under-five children with presumptive TB, adenitis, edema, and malnutrition status were strongly associated with TB confirmed diagnosis. Assessing malnutrition status should be a key component of pediatric TB screening.

**OA-02-511-21 Using a mobile application to improve presumptive tuberculosis identification in children in Western Kenya**

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**Background:** In Kenya and other low-and middle-income countries(LMICs), TB in children is often underdiagnosed and underreported. Healthcare workers in

pediatric outpatient clinics, overburdened with competing clinical priorities, forget to consider TB during their evaluations. Mobile health interventions like the presumptive pediatric TB mobile application(PPTBMAPP) show promise in improving pediatric presumptive TB screening. However, this application has never been formally evaluated.

**Design/Methods:** We used a mixed-methods implementation science framework to assess the PPTBMAPP for feasibility, appropriateness, and effectiveness. Using a participatory, iterative approach, the PPTBMAPP was piloted and adapted over 3 months utilizing feedback from qualitative interviews with healthcare workers in pediatric outpatient clinics of Webuye County Hospital in western Kenya. A community health volunteer(CHV) used the PPTBMAPP to screen children for presumptive TB in waiting areas. The PPTBMAPP incorporated five TB screening questions and alerted the CHV if the child met criteria for presumptive TB (two or more symptoms positive). The impact of PPTBMAPP on both presumptive and pediatric TB disease detection was assessed through register review for 6-month periods before and after PPTBMAPP implementation.

**Results:** Between 08/2019-01/2020, 1797 children ≤15 years were screened via the PPTBMAPP. Use of the PPTBMAPP resulted in a significant increase in the proportion of children recorded in the presumptive TB register(10.7% vs. 16.2%,  $p=0.000477$ ) and resulted in a trend toward increasing diagnosed TB in children(14.5% vs. 18.1%). During follow-up interviews, participants reported practice changes with the PPTBMAPP. “With TB diagnosis...at least we have opened up our minds. I think we are taking more and more history about TB.”

Register	Intervention Period		P-Value
	Pre (08/2018-01/2019)	Post (08/2019-01/2020)	
Presumptive TB	97/908 (10.7%)	160/989 (16.2%)	0.0005
Active TB Disease	17/117 (14.5%)	15/83 (18.1%)	0.5

Statistical significance determined using chi-square test

[Table. Proportion of children of total individuals in the presumptive and active TB disease registers at Webuye County Hospital]

**Conclusions:** These findings suggest that implementing mobile health applications to improve presumptive TB screening is feasible and can be used successfully by a CHV. The PPTBMAPP increases presumptive TB recognition in children and may be an effective tool in high TB burden countries like Kenya.

### OA-02-512-21 Protecting our children from active TB disease – expanding TB preventive therapy in nine sub-Saharan countries

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**Background:** TB preventive therapy (TPT) can reduce the likelihood of developing active TB disease for individuals at higher risk, such as child contacts of TB index cases. Despite being strongly recommended by the WHO, household contact investigation (HCI) and TPT remain poorly implemented. We evaluated the rate of TPT initiations in child contacts (0-4 years) before and after the introduction of intensified HCI for bacteriologically-confirmed TB index cases.

This work contributes towards achieving the END-TB strategy and the 2018 UN declaration goal on TB prevention and care.

**Design/Methods:** The intervention included 123 health facilities across nine sub-Saharan countries (Cameroon, Côte d'Ivoire, DRC, Kenya, Lesotho, Malawi, Tanzania, Uganda, and Zimbabwe). The intervention consisted of training and supporting health workers, including community health workers who perform household contact investigation, screening of children for TB symptoms at the household level, and the referral of them to health facilities for TB investigation or TPT initiation. Pre-intervention data (12 months) were retrospectively collected from facility registers beginning six months before extraction.

Post-intervention data of varying period lengths per site (mean= 9.8 months from start of intervention) were collected prospectively for the same facilities using a project form. Averages, proportions, and monthly rates were calculated using descriptive statistics. Pre- and post-intervention monthly rates comparison was done using T-Test analysis for two dependent means.

**Results:** The site-averaged monthly rates for TPT initiation of child contacts significantly improved by +177% in the intervention period (4.62) as compared to the pre-intervention period (1.67) ( $p < 0.0001$ ).

Additionally, 43% (53/122) of facilities reported their first pediatric TPT initiation following the start of CaP-TB. All TPT-eligible children identified through HCI were initiated on TPT.

**Conclusions:** HCI of child contacts under 5 years is feasible in routine clinical settings, can significantly improve TPT initiation for eligible children, and should, therefore, be prioritized for scale-up.

	Pre-Intervention (n=69)*	Intervention (n=69)*	% of Improvement	p Value
Average # months evaluated/site	12.0	9.8	N/A	N/A
Number of pediatric TPT initiations	1,383	2,922	N/A	N/A
Average monthly TPT initiation rate/site	1.67	4.62	+177%	$p < 0.0001$
Number of facility newly capacitated	N/A	53	N/A	N/A

\* 53 of the 122 sites sampled were newly capacitated in TPT initiation of contacts <5 years old through intervention and were therefore excluded from the pre-/post- intervention comparison.

[Table 1: TB preventive therapy initiation comparison, pre- and post-intervention]

### OA-02-513-21 Challenges and solutions for the recruitment of children to an MDR-TB prevention trial: Early experiences from TB-CHAMP

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**Background:** TB-CHAMP is a cluster randomised community-based placebo-controlled trial to assess the efficacy and safety of fluoroquinolone preventive therapy in children under 5 years, exposed to an adult with multidrug-resistant (MDR) tuberculosis (TB) in the household. Recruitment to randomised clinical trials can be challenging with dire financial, scientific and clinical consequences. Recruitment for blinded and placebo controlled paediatric TB prevention trials is particularly difficult, especially in settings with high population mobility.

**Design/Methods:** TB-CHAMP is being conducted at three South African sites in diverse communities. Adult pulmonary MDR-TB index cases diagnosed in the preceding 6 months are identified from laboratory database extracts and TB clinics/hospitals and pre-screened by re-

cruiting teams. Recruitment is tracked using a dedicated electronic recruiting platform. Research team questionnaires, workshop notes, recruitment diaries, and minutes of team meetings and calls were used to describe recruitment barriers and potential solutions.

**Results:** 4,187 adult index cases were identified between 1 September 2017 and 31 July 2019 at the three sites. Of 3,552 (84.8%) adults with pre-screening outcomes, 1597 (45.0%) reported no children under 5 years in the household, 562 (15.8%) had confirmed rifampicin mono-resistant TB, and 268 (7.5%) were uncontactable. 326 index cases (7.8%) were screened, 496 of their child contacts screened, and 449 children enrolled. Numerous barriers relating to the target population, study design, setting and study team/resources were identified. Thorough and flexible recruitment planning using current demographic and routine data, customized recruitment tracking data systems, a dedicated recruiting team with strong leadership, adequate driver and recruiter resources to recruit across large geographic areas, and excellent relationships with routine TB services emerged as key factors to ensure recruitment success.

**Conclusions:** Recruitment into MDR-TB prevention trials is challenging, especially in children. Several MDR-TB prevention trials are currently underway. Lessons learnt from TB-CHAMP will be relevant to these and future research efforts.

## OA-03 Optimising lung health beyond TB

### OA-03-514-21 Clinical predictors of outpatient child pneumonia mortality and development of a severity of illness score for outpatient care in rural Bangladesh – a multisite study

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**Background:** Identifying children at higher risk of pneumonia mortality during outpatient care may improve outcomes. We explored clinical predictors of child pneumonia mortality and developed a predictive model applicable to outpatient care in rural Bangladesh.

**Design/Methods:** From 2015-2017 we enrolled 3-35 month olds during a pneumococcal vaccine impact study at three Upazila Health Complex outpatient clinics in Sylhet, Bangladesh. Study physicians diagnosed clinical pneumonia per 2014 World Health Organization integrated management of childhood illness guidelines. Outcomes were assigned thirty days after diagnosis. We explored clinical predictors of mortality with logistic regression models adjusted for clinic, age, and sex and developed multiple scores after considering regression results and applicability of clinical features to outpatient care. We undertook model selection using c-statistic and Bayesian information criterion (BIC).

**Results:** We evaluated 10,145 outpatient pneumonia cases. Mortality was 0.5% (n=47). Malnutrition, chest indrawing, grunting, low oxygen saturation, and general danger signs were independently associated with mortality. The most parsimonious model with the highest c-statistic for mortality (0.80), and most favorable BIC, included moderate or severe malnutrition by weight-for-age and abnormal oxygen saturation.

**Conclusions:** We successfully developed a pragmatic score predictive of mortality using non-invasive clinical features applicable to outpatient pediatric care in rural Bangladesh.

### OA-03-515-21 Pneumococcal serotype epidemiology in Botswana following the introduction of 13-valent pneumococcal conjugate vaccine

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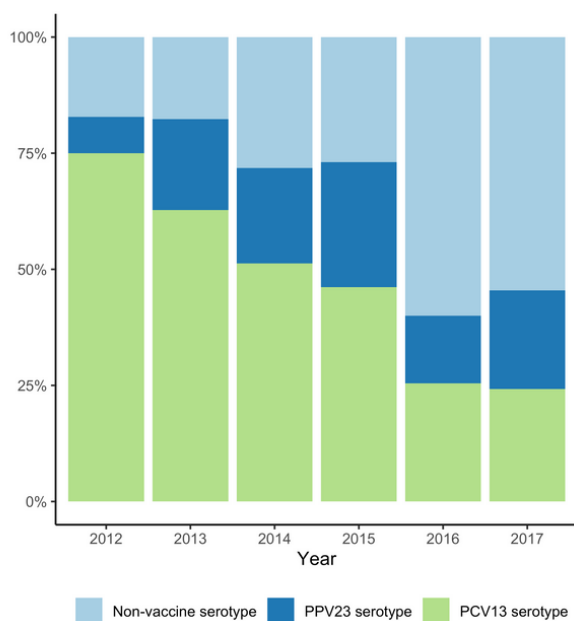
**Background:** Invasive pneumococcal disease (IPD) is responsible for over 300,000 child deaths worldwide each year, and most occur in low- and middle-income countries. The addition of pneumococcal conjugate vaccines to national immunization programs reduced the burden of IPD, but the sustained effect of vaccination may be hampered by an increase in colonization and disease caused by non-vaccine serotypes.

We sought to describe temporal trends in pneumococcal serotype colonization among children in Botswana following the introduction of 13-valent pneumococcal conjugate vaccine (PCV-13).



**Design/Methods:** PCV-13 was introduced in July 2012. We collected nasopharyngeal samples from two studies of children under 2 years of age with and without pneumonia between 2012 and 2017. We identified *Streptococcus pneumoniae* through PCR targeting the *lytA* gene and pneumococcal serotypes through real-time PCR. We used multinomial logistic regression to evaluate for a relationship between year and serotype category (PCV-13 serotype vs non-PCV-13 serotype) after adjusting for age and HIV status.

**Results:** 268 pneumococcal strains from 221 children were included in this analysis. The mean age of children was 8 months and 32% were either HIV-infected or HIV-exposed, uninfected. PCV-13 serotypes accounted for 75% of the identified serotypes in 2012 but only 24% of serotypes by 2017. In adjusted analyses, the likelihood of a strain being a PCV-13 serotype declined by 37% per year during the study period (relative risk: 0.63; 95% confidence interval: 0.53, 0.75). The majority of non-PCV-13 serotypes identified are not present in the 23-valent pneumococcal polysaccharide vaccine (PPV23).



[Figure. Vaccine and non-vaccine serotypes by year]

**Conclusions:** The introduction of PCV-13 in Botswana was associated with a significant decline in colonization by vaccine serotypes. Serotype replacement most commonly occurred with serotypes that are not covered by any available pneumococcal vaccine. Understanding pneumococcal serotype epidemiology in settings with the highest burden of disease is essential to optimizing the next generation of pneumococcal vaccines and reducing IPD-associated mortality.

## OA-03-516-21 Mycobacteria and other acid fast organism among presumptive pulmonary tuberculosis patients in Kaduna state, Nigeria

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**Background and challenges to implementation:** Mycobacteria tuberculosis (MTB) remains the leading cause of death from a single infectious agent globally. Several other species of Mycobacteria have been isolated in humans but the prevalence has not been documented. Tuberculous and Non-tuberculous mycobacteria (NTM) sometimes present both diagnostic and treatment dilemmas to Health care workers due to similar characteristics and clinical symptoms. This study investigated the phenotypic characteristics of Mycobacteria isolates recovered from clinical specimens of presumptive TB patients in Kaduna state Nigeria.

**Intervention or response:** Two thousand, two hundred and twelve (2212) sputum samples were collected from patients clinically suspected to have TB from the three TB service delivery points in Kaduna Sate, Nigeria between May 2017 and October, 2018. Samples were processed by decontaminating with 4% NaOH-Citrate N-acetyl-L-Cystein method before conventionally inoculating them unto Lowenstein Jensen (L.J) culture slants and incubated at 37°C for 8 weeks. Cultures positive for acid fast bacilli (AFB) by ZN stain were further analyzed with a rapid TB antigen assay (SD-Bioline) to differentiate Mycobacterium tuberculosis complex (MTBC) from Non tuberculous mycobacteria (NTM).

**Results/Impact:** Out of the 2212 presumptive TB patients, 300 (13.6%) were positive for AFB by microscopy. Of the 300 AFB positive samples, 272 (91.0%) were culture positive on LJ medium, 18 (6.0%) were culture negative and 10 (3.0%) were culture contaminated. Result of the distribution of mycobacteria among infected patients within the study area revealed that 219(80.5%) were infected with MTBC, 42 (15.4%) with NTM and 11 (4.0%) with both MTBC and NTM.

**Conclusions:** A relatively high rate of TB in the study area was caused by NTM. The National TB Programme should integrate Rapid specific diagnostic test for identi-

fication of MTBC and NTM in diagnostic algorithm for patients with smear-positive sputum before treatment is initiated.

### OA-03-517-21 A novel quantitative tool for rapid monitoring of *Mycobacterium abscessus* pulmonary disease treatment response

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**Background:** *Mycobacterium abscessus* is the most common rapid growing (RGM) non-tuberculous mycobacteria (NTM) causing NTM pulmonary disease (PD). Treatment involves long and toxic multi-drug regimens with uncertain benefit. It is difficult to assess antibiotic efficacy as current treatment monitoring depends on semi-quantitative culture of serial clinical samples that takes weeks to provide results.

We have developed an assay, the molecular bacterial load assay (MBLA) for *M. abscessus*. The MBLA targets the species-specific portion of 16S ribosomal RNA region using real-time reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) aiming to accurately and rapidly quantify the viable bacterial load from patients' sputum samples. We aim to validate *M. abscessus* MBLA as a treatment monitoring tool for *M. abscessus*.

**Design/Methods:** The limit of detection was obtained using serial dilutions of RNA extractions alongside CFU plates. RT-qPCR optimisation was performed through comparing serial dilutions of the same sample under different conditions. Assay selectivity was tested through RT-qPCR of DNA of other common pulmonary pathogens. Patient samples from NHS Scotland are under evaluation currently.

**Results:** The MBLA showed a limit of detection of 10 CFU/ml. Following RT-qPCR optimisation, the reaction efficiency was 96%. It did not detect any of the common respiratory pathogens tested. Initial patient sample results overall matched those from the current gold standard, mycobacteria growth indicator tube (MGIT). MBLA results could be obtained in hours in comparison to culture-based methods where positivity could be delayed for up to 21 days.

**Conclusions:** *M. abscessus* MBLA is a species-specific test with a low limit of detection and high efficiency. The *M. abscessus* MBLA is the first molecular quantitative treatment monitoring tool applicable to NTMs. It does not require decontamination and results could be

available on the same day. Trials to monitor treatment response in patients with *M. abscessus* infection are underway.

### OA-03-518-21 How does exposure to fine particulate matter in Malawi vary by gender, exposure source, and cooking characteristics? Fine-grain data from an ethnography-linked exposure study

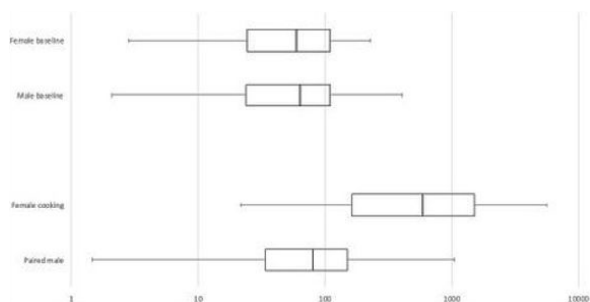
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**Background:** Air pollution exposure through the life course contributes to a range of respiratory pathology in adults and children, including acute infections and non-communicable diseases. In Malawi a great majority of the population use solid fuels for cooking, causing frequent exposure to high concentrations of air pollution including fine particulate matter (PM<sub>2.5</sub>). We use personal air quality data to describe PM<sub>2.5</sub> exposures by gender, exposure source and cooking features in a Malawian village.

**Design/Methods:** Reported exposure data comprise a preliminary analysis of data from a mixed methods study of air pollution in rural Malawi. Researchers spent extended periods of time over seven months alongside men and women living in the village. Portable monitors worn during a range of activities captured real-time PM<sub>2.5</sub> data (µg/m<sup>3</sup>) on cooking and other exposures. The resulting 203 hours of data and 6 104 datapoints were analysed in Stata V15.1 using appropriate statistical methods.

**Results:** Thirty-one exposure intervals were included for female participants; fourteen paired with a male counterpart. For women, median [IQR] PM<sub>2.5</sub> levels differed significantly between cooking 418.8 [143.3-926.7], other exposures 106.6 [57.4-369.2] and baseline (no identified source) 35.2 [21.7-50.7], p=0.001. Paired male data revealed similar median PM<sub>2.5</sub> levels to their female counterparts at baseline (39.7 [21.7-47.2]), but without the large cooking-related increases experienced by women: median 46.5 [32.3-70.7] and 38.8 [32.4-51.1] while women cooking and performing other activities respectively.

Biomass was used for all cooking activity. Mixed model regression analysis adjusting for activity, fuel, cooking device, and location showed that lowest cooking related PM<sub>2.5</sub> levels were associated with use of cookstoves in well ventilated spaces (typically an unwallled veranda).



[Figure.]

**Conclusions:** Cooking constituted the main PM<sub>2.5</sub> exposure source in this setting. The subsequent gender disparity in exposures is a key finding. Data on variables influencing exposure levels will inform a village-based clean air intervention.

### OA-03-519-21 Pulmonary function testing and predictive equations in a healthy adult population in Mbeya, Tanzania

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**Background:** Many African countries have a disproportionately large burden of infectious respiratory diseases. The use of spirometry testing in research as well as in diagnosing and managing of those diseases has led to an increased need for locally derived reference equations. These local data are important for interpreting pulmonary function test results and deciding on the management strategies of pulmonary diseases. This study aimed at establishing lung function values and predictive equations for a healthy, non-smoking adult population living in Mbeya, Tanzania.

**Design/Methods:** This cross-sectional study was conducted in Mbeya, in the Southern Highlands of Tanzania. Healthy participants underwent a socio-demographic interview, anthropometric measurements, as well as a lung function test using a hand-held spirometer. Data were analysed using descriptive statistics and logistic regression to develop predictive equations.

**Results:** A total of 400 males and females took part in the study. From them, a total of 343 (85.8%) participants had usable spirometry results, after applying the ATS/ERS reproducibility and acceptability criteria. Mean age of participants with valid spirometry results was 32.7 (18, 71.5) with 189 males and 154 females. Mean FVC in litres was 3.52 (1.01, 6.50) and mean FEV1 in litres was 2.95 (0.55, 4.94). We generated the predictive Tanzanian equations and compared them to only one existing

Tanzanian reference standard, derived from a smaller cohort, as well as GLI equations. The GLI equations overestimate the spirometry values for the given sex, age and height in our studied population. Meanwhile, previous Tanzanian equations significantly underestimate the spirometry values.

**Conclusions:** This study provides predictive equations for spirometric pulmonary function in a healthy, non-smoking Tanzanian population. Incentive was to compare them to other widely-used standards such as GLI and to the only other Tanzanian study. The established equations and references will be used in the analysis of the TB Sequel Project spirometry data.

### OA-03-520-21 Availability of diagnostic services and essential medicines for non-communicable respiratory diseases in African countries

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**Background:** The burden of asthma and chronic obstructive pulmonary disease (COPD) is increasing and has become a worldwide public health issue. In Africa the management of these diseases is challenging and likely affected by the availability of appropriate diagnostic tests and essential medicines. The aim of this study was to explore the availability of diagnostic services and essential medicines for non-communicable respiratory diseases (NCRDs) in African countries.

**Design/Methods:** Questionnaires were self-completed by healthcare workers attending the Pan African Thoracic Society Methods in Epidemiology, Clinical and Operations Research (PATS MECOR) and International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPALA) meeting. Information was obtained on the availability of diagnostic spirometry and essential medicines for asthma and COPD at their healthcare facility. Data were analysed by simple descriptive statistics and open answer questions coded.

**Results:** 37 questionnaires were returned representing 13 different African countries. The availability of diagnostic spirometry was 73.0%, although within this sample 33.3% faced sporadic availability due to maintenance issues. Among several factors, the most common reasons



for non-availability were lack of knowledge about spirometry and its utility in practice. The availability of essential medicines ranged from 37.8% for ICS-LABA inhalers to 100% for prednisolone 5mg tablet. Medicines were sometimes unavailable due to supply chain difficulties.

**Conclusions:** Availability of diagnostic spirometry and essential medicines for COPD and asthma in these African countries is varied and generally below World Health Organisation (WHO) targets. The results add to the few available studies on the availability of these resources in Africa. Conclusions based on meeting attendees, from mainly urban and national level facilities, may not be generalisable within African settings. However, thematic analysis revealed common barriers to availability that could inform much-needed corrective strategies if explored more thoroughly in each country.

### OA-03-521-21 Chronic lung diseases remain under-prioritized in Africa despite their growing burden: findings from a lung health policy analysis

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**Background:** Globally, 4 million people die prematurely from CLDs (e.g. asthma and chronic obstructive pulmonary disease (COPD)) (Global Impact of Respiratory Disease – Second Edition, 2017). In sub-Saharan Africa (SSA), the burden of CLDs is estimated to be large and growing (Bigna and Noubiap, 2019). This study seeks to provide evidence on CLD policy and programme responses, prioritised CLDs, health system approaches to address CLDs, and CLD financial investments in East Africa, focusing on Kenya and Uganda.

**Design/Methods:** We conducted a desk review of CLD-relevant policies at regional level (East Africa) and national level for Kenya and Uganda. Interviews with lung health stakeholders in Uganda and Kenya were conducted to contextualise findings from the desk review. This paper fills an evidence gap on lung health policy in SSA and will inform future CLD research, policies, and programmes.

**Results:** Preliminary findings reveal no CLD-specific policies in East Africa, Kenya or Uganda and a narrow focus of lung health policies on tuberculosis. East African policies do not name CLDs however national-level

policies refer to CLDs, namely COPD and asthma. The main approach to CLD control in the two countries is prevention by addressing their risk factors (e.g. tobacco exposure and poor air quality). Documentation of CLD financial investments was not available. Interviews revealed political will, but insufficient resources to manage CLDs.

**Conclusions:** We found a lack of CLD policy prioritization in Kenya, Uganda, and East Africa. The narrow focus of lung health policy investments on tuberculosis calls for local evidence on CLDs' disease burden, economic burden, and interventions to address their risk factors, as well as effective research translation initiatives to drive policy action. Given SSA's resource-constrained context, investments must be evidence-informed to ensure resource allocations are commensurate to the scope of the problem and proven to improve management and prevention of CLDs.

### OA-04 A holistic approach: experiences from Europe

#### OA-04-522-21 "You have to adjust your whole life": interconnected, dynamic influences on adherence to treatment for tuberculosis among adults in three UK cities

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**Background:** Tuberculosis (TB) incidence in the United Kingdom (UK) is declining but remains disproportionately high in immigrants and the socioeconomically disadvantaged. TB treatment is lengthy and arduous; there

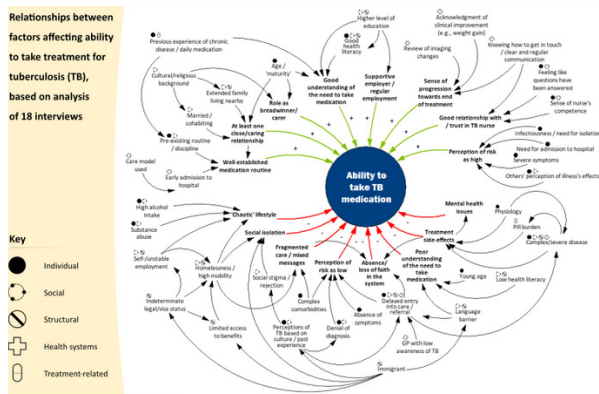
is a need to understand factors affecting patients' ability to stay on treatment, but most qualitative research on TB treatment adherence stems from high burden settings. This study explored the experiences of individuals on TB treatment in three UK cities.

**Design/Methods:** Eighteen adults (six female) who were taking or had previously taken treatment for TB and provided informed consent were interviewed in person using a topic guide that explored social and medical circumstances and experiences of TB care. Transcripts were analysed using an adapted framework method that classified factors affecting treatment-seeking trajectories into individual, social, systems, and structural issues.

**Results:** Eleven of 18 individuals were immigrants (from South/East Asia and sub-Saharan Africa); a further four were UK-born Black, Asian, or Minority Ethnic. TB and treatment-taking were often experienced as hugely disruptive, affecting individuals in multiple interrelated ways.

In addition to debilitating symptoms (fatigue, loss of strength, pain), treatment side-effects (nausea, altered consciousness), and stigma, participants also dealt with threats to income, family responsibilities, unstable housing, social and physical isolation, worsening mental health, and damaged relationships.

Those who had a strong support network, stable employment, a firm routine adaptable to medicine-taking, a good relationship with their TB team, and a robust understanding of the need for treatment reported finding it easier to maintain a daily medication-taking habit (Figure).



[Figure.]

**Conclusions:** An individual's ability to take treatment for TB does not remain constant over time and is susceptible to complex, interconnected social and structural 'disruptors' outside the control of the individual or health system. Comprehensive needs assessment prior to treatment initiation (with periodic re-evaluation) and supportive approaches that consider individual, social, and structural circumstances may help improve adherence.

### OA-04-523-21 Doubling tuberculosis preventive treatment enrollment rates among people living with HIV in Ukraine

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**Background and challenges to implementation:** People newly diagnosed by infectious disease specialists with HIV infection require TPT to reduce the risk of developing TB disease. Currently only TB doctors can prescribe TPT in Ukraine, therefore PLHIV must visit a TB facility to access TPT. This practice is inconvenient for PLHIV, puts the patient at increased risk of acquiring TB, and could mean patients do not access TPT services at all.

**Intervention or response:** Under the CTB project, PATH introduced and piloted a revised model for the prescription and management of TPT for PLHIV in Donetsk oblast. Following an assessment, data analysis, and advocacy meetings with local authorities to share the latest international recommendations, local regulations and procedures were revised and endorsed by the oblast government in January 2019, allowing infectious disease specialists to prescribe TPT, order medicines for TPT, and monitor the safety of TPT.

**Results/Impact:** In 2018 (pre-intervention), only 30% of PLHIV started TPT (404 out of 1,340), while 86% (939 out of 1,097) were enrolled in 2019 (post-intervention). By shifting TPT management to HIV specialists, the percentage of PLHIV starting TPT increase steadily, from 30% as of end 2018, to 63% (154 out of 246) as of March 1, 2019, and 78% (422 out of 542) as of June 1, 2019.

**Conclusions:** Adapting oblast-level policies to enable HIV specialists to oversee TPT for PLHIV more than doubled the number of PLHIV started on TPT. Policy shifts also included revisions to evaluate the quality of TPT services, TPT completion and development of TB disease among PLHIV based on TPT completion. This pilot also highlighted the effectiveness of data-driven, evidence-based, and solution-oriented advocacy to facilitate rapid policy changes to improve TB/HIV service delivery. Lessons from this pilot will be used to advocate for similar changes in other oblasts to increase TPT uptake and improve outcomes among PLHIV in Ukraine.

### OA-04-524-21 Providing incentives and enablers to support people suffering with TB completing their treatment in Belgium: a successful approach

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**Background and challenges to implementation:** In Belgium, a low-incidence country (8,6 TB cases/100 000 inhabitants), overall TB treatment success rate is below the 85% WHO target (average of 80,3% in 2015-2017). Like in most European countries, we observe an increasing proportion of hard to reach/hard to treat among people affected by TB. In Brussels, homeless account for 19,2% of all TB patients. This population experiences high risk of adherence problems and needs support to complete their treatment.

**Intervention or response:** In 2015, started a joint project between BELTA (Belgian TB program) and Damien Foundation in Brussels, aiming at providing incentives and enablers to help the most vulnerable people with TB fulfilling their basic needs and therefore enabling them to complete their therapy.

According to their situation, patients were offered different types of support:

- Transport tickets to facilitate patient access to medical appointments
- Social vouchers to buy food or essential products for motivating patients to show up at their appointments
- Renting a bed in a homeless shelter the whole length of treatment with the prerequisite for homeless patients to follow treatment recommendations.

All patients enrolled were recorded in a specific database for monitoring.

**Results/Impact:** Since 2015, 170 patients were enrolled and received at least one incentive. One hundred twenty-five (83%) completed treatment. Considering only people benefitting from a shelter (69), 63 (94%) completed treatment. Besides overcoming patient's basic needs, thus motivating for better compliance, this supporting project helps building trustful relationship between patients and TB nurses, which is also crucial for adherence.

**Conclusions:** This project, through enablers/incentives, and especially shelter, demonstrated its effectiveness in supporting "hard to treat" patients in completing their TB treatment. This approach has an undeniable cost but is largely balanced by preventing expensive multidrug-resistant treatment. For sustainability, advocacy is needed to involve stakeholders.

	Patients who received any type of incentives/enablers N patient (%)	Patients who were hosted in shelter N patient (%)
Cured	125 (83,3%)	63 (94%)
Lost to follow up	8 (5,3%)	1 (1,5%)
Left Belgium or transfer	15 (10%)	2 (3%)
Refusal of treatment	1 (0,7%)	1 (1,5%)
Deceased	1 (0,7%)	0 (0%)
Total	150 (100%)	67 (100%)
Still under treatment	20	2
Grand total	170	69

[Table 1. Treatment results for patients enrolled between 2015 and 2019]

### OA-04-525-21 Video observed treatment for TB patients in Belarus

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**Background and challenges to implementation:** Video observed treatment (VOT) is in line with both components of proper management of TB patients: people-centered integrated care and e-health approach. In Belarus with the Global Fund's support a pilot VOT project was expanded across the country in October 2016.

**Intervention or response:** TB patients were provided with smartphones and internet access, and instructed on how to record and transmit video files to trained clinic staff. Measures to monitor VOT treatment prospectively in the countrywide cohort were developed.

**Results/Impact:** By April 1, 2020, 1273 TB patients across the country were recruited: median age 38 years; 65% male; 53% employed, 4% students, 39% unemployed, 4% on maternity leave; 41% with DS-TB, 59% with RR/MDR-TB, including 15% with XDR-TB. Final treatment outcomes were recorded in 816: DS-TB (n=656) treatment success - (99%); RR/MDR-TB (n=160): treatment success - 87%. In both cohorts lost to follow up was 2% only (12% - in country wide cohort).

**Conclusions:** In addition to high levels of patient acceptability and treatment adherence, VOT for TB patients in Belarus demonstrates excellent treatment outcomes.

### OA-04-526-21 ART prescription by TB doctors in Odeska oblast, Ukraine - successful model of integration of services for patients with TB/HIV co-infection

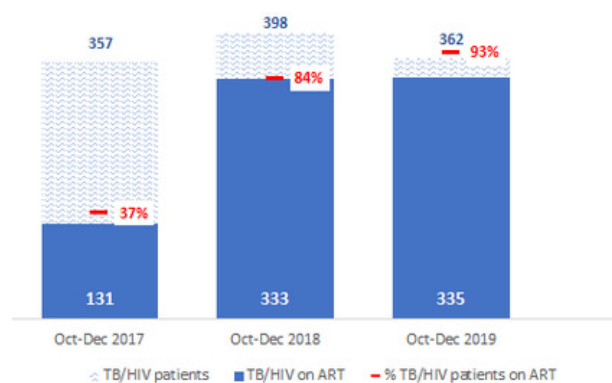
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**Background and challenges to implementation:** Chance of survival is increased nearly six-fold for patients with TB/HIV co-infection who receive ART early. In Odeska oblast, where almost a half of TB patients are HIV infected, ART coverage reached only 37% in the end of 2017, and the average time from HIV diagnosis to initiation of ART was 48 days. The CTB project found that the main barrier in ART provision for patients with TB/HIV was distant ART services. In Ukraine, only HIV specialists located at oblast centers prescribe ART, which leads to delayed initiation and low ART coverage among TB patients.

**Intervention or response:** CTB worked with the Odeska oblast health team to pilot a new approach for ART provision. CTB provided trainings on ART prescription and on-the-job support to TB doctors. For the first time in Ukraine, TB doctors independently started to prescribe ART for patients with TB/HIV and received access to the medical information system for HIV allowing them to enter data and register patients directly.

**Results/Impact:** We observed a reduction of number of days for ART initiation from 48 days to 17 days and an increase of ART coverage from 37% (Q4 2017) to 93% (Q4 2019).

The best practices and experience of Odeska oblast then have been disseminated to other oblasts supported by CTB and PEPFAR. ART coverage among patients with TB/HIV coinfection in all of these oblasts has now improved to more than 90% (see Figure).



[Figure.]

**Conclusions:** The findings clearly indicate that integrating TB and HIV services by providing access to HIV services where patients get TB care can substantially increase ART coverage rates and ensure early initiation

of ART among TB patients. Prioritizing the scale up of integrated services across Ukraine will reach more patients with more effective treatment and reduce TB/HIV mortality and improve treatment efficiency.

### OA-04-527-21 Results of pilot of integrated diagnosis of TB and HCV among HIV-positive incarcerated individuals using GeneXpert in Dnipropetrovska oblast of Ukraine

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**Background and challenges to implementation:** As of 2019, 3,860 HIV-infected individuals, 176 of whom had HIV/TB co-infection, were registered within the Center of Health Care of the Ministry of Justice of Ukraine. In prisons before 2019, GeneXpert machines were used only for TB. Therefore, the USAID Serving Life project implemented by PATH, procured a GeneXpert machine and cartridges for TB and HCV diagnosis and HIV viral load (VL) determination using rapid molecular genetic testing. The integrated patient-centered diagnosis approach was first piloted in a Ukrainian prison.

**Intervention or response:** During 2019, 242 HIV-infected detainees and prisoners were screened for TB and 73 (30.1%) with risk had TB tests using GeneXpert. All 242 participants were screened for HCV with a rapid test and 168 (69%) with positive tests were forwarded for GeneXpert HCV VL testing. HIV VL determination was conducted for 166 eligible (69%) HIV-infected individuals. Services were provided in the prison where participants reside, and results provided within 2 hours.

**Results/Impact:** Thirteen individuals (17.8%) were diagnosed with TB; 6 with DRTB. 140 individuals (84%) had a confirmed HCV diagnosis and determined VL level. 63 individuals (38%) had an undetectable HIV VL. Simultaneous HCV and HIV VL tests were done for 134 individuals (110 HCV positive; 50 undetectable HIV VL); joint TB and HIV VL tests for 3 individuals (0 TB positive; 2 undetectable HIV VL); HCV, TB and HIV VL comprehensive diagnosis for 15 individuals (2 TB positive; 14 HCV positive; 8 undetectable HIV VL); and 2 people of 15 had HIV/TB/HCV co-infection.

**Conclusions:** The pilot confirms high prevalence of TB and HCV among HIV-positive individuals and need for an integrated patient-centered approach to early diagnosis. The Ministry of Justice of Ukraine plans to procure cartridges to scale up the approach in penal facilities that has the potential for system efficiencies, cost savings, and improving patient-centered services beyond penal settings.

### OA-04-528-21 COVID-19/TB (MDR-TB) co-infection in Belarus

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**Background and challenges to implementation:** The first case of COVID-19 in Belarus was registered in Minsk on 28 February 2020. As of 10 May 2020, a total of 22,973 confirmed cases have been reported, including 6,406 recoveries and 131 deaths, more than 263,000 COVID-19 PCR tests have been conducted. Belarus also is one of the high burden MDR-TB countries in the world. The Ministry of Health and National TB Control Program closely monitor the possible overlapping of COVID-19 and TB (MDR-TB) epidemics.

**Intervention or response:** All patients in the country with COVID-19/TB(MDR-TB) co-infection are registered and admitted in the TB inpatients facilities. Measures to monitor COVID-19/TB (MDR-TB) patients prospectively in the countrywide cohort were developed. Seven COVID-19/TB (MDR-TB) were registered as of 10 May 2020.

We observed difficulties in diagnosis due to similar clinical symptoms and lung lesions, and in treatment due to drug interactions. Early testing and following the infection prevention and control measures in the TB facilities are important to prevent further spread of COVID-19. Video supported treatment will be used to ensure adherence of patients on ambulatory care. The country is preparing a funding request to the Global Fund for additional funding for COVID-19 response.

**Results/Impact:** As a result of the project, we expect to receive data on:

- 1) incidence of COVID-19 among TB(MDR-TB) patients;
- 2) severity of COVID-19 disease in TB(MDR-TB) patients;
- 3) effect of BCG vaccination in the past on COVID-19 manifestations,
- 4) details of COVID-19 lung damage on the ground of TB lung lesions;
- 5) adverse events of the drugs and their interactions; and finally 6) treatment outcomes for both infections.

**Conclusions:** We hope our data will help create a global database for the subsequent generation of evidence-based recommendations to combat both infections.

### OA-05 Innovative TB diagnostics

#### OA-05-529-21 Correlation of high-sensitivity C-reaction Protein, Gene Xpert and urine LAM test for TB diagnosis in HIV+ Kenyan patients within DREAM program

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**Background:** TB has a high prevalence and mortality, representing the leading cause of death in HIV+ people. WHO reports that in Kenya, 40,000 HIV+ patients were newly diagnosed with TB in 2018. In 2016 only 63,4% of people with TB worldwide were notified. The objective of the present study is to improve TB diagnosis among HIV+ patients. HS-CRR, LF-LAM test, 4SS and Gene Xpert will be evaluated.

**Design/Methods:** IDEA (Innovative Diagnostic Enhancement Against) TB is a prospective study aimed to evaluate new diagnostic tools for TB in HIV+ patients. HIV+ consecutive adult patients attending the sites of the study (DREAM Centers in Meru/Nchiru, Chaaria, Nkubu) who were clinically suspected of having TB and referred for Gene Xpert were enrolled. Each participant was entered in the datasheet (demographic, anthropometric and clinical data) and tests were performed: urinary LF-LAM-test, serum HS-CRP and Gene Xpert on sputum.

**Results:** 578 TB suspected patients were enrolled. 62,8% (363/578) were female, the median age was 46 years ( $\pm 12,5$ ), 24,9% (144/578) patients were malnourished, and the mean CD4 count and Viral Load were respectively 477 cells/ml ( $\pm 302$ ) and 0,5 log ( $\pm 1,4$ ).

TB suspect was confirmed only on 86 (14,9%) patients (either LAM or Xpert positive test). Concordance between Xpert and LAM test was 87,3%.

HS-CRP was significantly higher in TB patients (35,0 mg/L vs 9,1 mg/L,  $p < 0,000$ ) (Figure 1).

Significant correlation was observed among HS-CRP and urine LAM test result ( $p < 0,000$ ) (Figure 2). No associations were observed with Xpert result levels.

In a multivariate analysis, only malnutrition and plasmatic HS-CRP higher than 20 mg/L were independently associated with TB diagnosis (adjusted OR respectively 2,2 [1,23-3,90] and 6,8 [3,75-12,60]).

**Conclusions:** Diagnosing TB infection in HIV+ patient remains challenging, as concordance with clinical screening and different tests is suboptimal. HS-CRP could play a role in TB diagnosis in HIV+ patients.

### OA-05-530-21 Purification of lipoarabinomannan from urine of patients with tuberculosis

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**Background:** Lipoarabinomannan (LAM) is a component of the Mycobacterium tuberculosis (MTB) cell wall commonly excreted in the urine of infected patients, offering great promise as a diagnostic biomarker of active tuberculosis (TB). However, LAM-based assays have limited diagnostic accuracy. The antibodies used in these assays are developed using LAM from cultured MTB cells. However, studies have shown its structure differs to that of urinary LAM (uLAM). Thus, there is a need to develop new antibodies with specificity to uLAM. To address this, we have developed a method for the purification of uLAM from patient urine that may be suitable for the generation of novel antibodies.

**Design/Methods:** We evaluated various methodologies to purify uLAM, including ultrafiltration, proteinase K digestion, chloroform and hot phenol extractions, Melon™ gel, affinity chromatography using protein G and concanavalin A, and size exclusion chromatography (SEC). These methods were evaluated individually, and the most optimal were assessed in combination using a 500 mL pooled urine sample from multiple TB patients and healthy individuals. Performance was evaluated for uLAM recovery and by total protein removal.

**Results:** We determined a multi-step approach including ultrafiltration to concentrate uLAM and remove salts and most urine components, resulting in recovery of 98% uLAM. However, with a total of 70 mg protein remaining, a combination of proteinase K digestion, chloroform extraction, concentration, and SEC was necessary. Overall, when these steps were sequentially applied to the urine sample, up to 51% of uLAM was recovered and 99% of total protein was removed.

**Conclusions:** We successfully developed an approach to extract and purify uLAM from clinical urine specimens which can be scaled to extract more uLAM from larger volumes. The resulting uLAM will be used to support generation and screening of new uLAM antibodies that may increase the sensitivity of TB LAM assays.

### OA-05-531-21 Sequence-specific hybridization capture of urine cell-free DNA to diagnose pulmonary tuberculosis

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**Background:** There is an urgent need for rapid tuberculosis (TB) diagnostic tests that do not rely on sputum. Urine cell-free DNA (cfDNA) is a promising TB biomarker, but is challenging to detect due to the short length (<100 base pairs) and low concentration of TB-specific fragments. We aimed to increase the sensitivity of TB diagnosis from urine by designing an assay that improves detection of short TB-specific cfDNA.

**Design/Methods:** We developed and optimized an ultra-sensitive hybridization capture method that uses sequence-specific DNA probes immobilized on magnetic beads to purify fragments of IS6110, an insertion sequence specific to the Mycobacterium tuberculosis complex. Purified TB-specific cfDNA was amplified using short-target qPCR (40 base pairs). We tested the assay on frozen urine specimens from adults in South Africa (n=34 with pulmonary TB, n=8 without TB) and in the United States (n=14 without TB). We determined assay sensitivity and specificity using sputum GeneXpert MTB/RIF as the reference standard. The assay operator was blinded to the GeneXpert results during urine analysis.

**Results:** The hybridization capture method increased recovery of short cfDNA (>90% recovery of 25-50 bp fragments) compared to a silica resin-based extraction method used previously for TB urine cfDNA. Paired with short-target qPCR, hybridization reliably detected ≤1 copy/mL of DNA spiked into 10 mL urine. In preliminary clinical testing, the assay detected TB-specific cfDNA in 27 of 34 (79%; 95% CI: 62-91%) urine samples from adults with pulmonary TB. Diagnostic sensitivity was 83% (20/24) in HIV-positive patients and 70% (7/10) in HIV-negative patients. Specificity was 100%, with no TB-specific cfDNA detected in urine from TB-negative adults from South Africa (n=8) or healthy controls from the United States (n=14).

**Conclusions:** Our hybridization capture assay detects TB-specific urine cfDNA with high sensitivity and specificity and may enable rapid, non-sputum-based diagnosis of active TB in both HIV-infected and HIV-uninfected populations.



**OA-05-532-21 Correlation between the metabolic urine profile using the nuclear magnetic resonance spectrometer and standardized case definitions for the diagnosis of childhood tuberculosis**

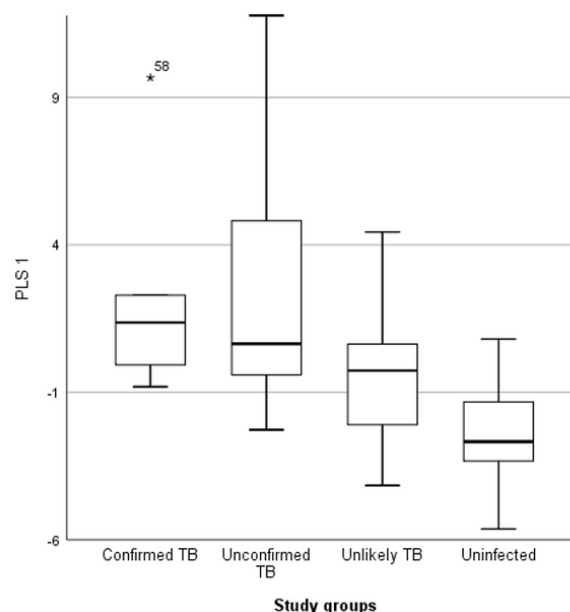
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**Background:** Ninety (90) percent of children who die of TB worldwide were not treated. Due to the lack of a reference test for TB diagnosis, most children are diagnosed by clinical scoring systems limited by the clinical presentation of the disease that often overlaps with similar clinical manifestations caused by other respiratory infections. Early diagnosis of TB is crucial for prescribing prompt treatment and reducing mortality. We aimed to characterize a urinary metabolic pattern in children with presumptive TB and associate it with the agreed standardized case definitions for the diagnosis of childhood TB.

**Design/Methods:** 63 children with TB suspicion who attended a hospital and 55 healthy children screened from a school. Children were classified according to the following clinical criteria: bacteriological confirmation, symptoms and signs, TB exposure, latent infection with Mycobacterium tuberculosis, compatible chest radiography, and response to TB treatment. We acquired urine spectra using NMR spectroscopy and applied a Partial least squares discriminant analysis (PLS-DA) to maximize the covariance between urine spectra of children with TB and those uninfected.

**Results:** Six (9.52%) children were classified as TB confirmed, 49 (77.78%) as TB unconfirmed and 8 (12.70%) as unlikely TB. Of them, 27 (43.55%) met three criteria, 17 (27.42%) met two criteria, 10 (16.13%) met four criteria, and 8 (12.90%) met one criterion consistent with TB. We identified a correlation between the PLS scores of the urine spectra and the standardized case definitions

used to classify TB cases. Thus, as the number of clinical criteria of children with presumptive TB decreased, the PLS scores became more similar to those of uninfected children (Figure 1).



[Figure 1. The box plot shows the correlation coefficients between partial least squares discriminant analysis (PLS-DA) scores and study groups according to the case definitions for childhood TB diagnosis. The central horizontal line within the boxes represents the median. The boxes comprise the two middle quartiles, and tiles indicate the 10th and 90th percentiles.]

**Conclusions:** There is a correlation between the urinary metabolic profile and case definitions for childhood TB diagnosis. This NMR-based urine metabolic profile may improve childhood TB detection by shortening the time of diagnosis and initiation of treatment.

**OA-05-533-21 A novel urine method for the diagnosis of active pulmonary tuberculosis by immunoassay for the detection of esat-6 using hydrogel nanoparticles in HIV patients**

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**Background:** In HIV patients, conventional tests have low sensitivity, we propose a new diagnostic test with NIPAM dye reactive blue, allowing capture, preservation and concentration of ESAT-6 in urine. NIPAs are copolymers which capture low molecular weight proteins and protect from enzymatic degradation.

	All HIV patients			HIV $\leq 200$ CD4 cells/mm <sup>3</sup>			HIV $> 200$ CD4 cells/mm <sup>3</sup>		
	Esat-6 NIPAm	Smear ZN	Ogawa Culture	Esat-6 NIPAm	Smear ZN	Ogawa Culture	Esat-6 NIPAm	Smear ZN	Ogawa Culture
<b>AUC</b>	0.75 (0.66-0.84)	0.69 (0.61-0.77)	0.73 (0.64-0.81)	0.78 (0.66-0.90)	0.68 (0.59-0.77)	0.73 (0.63-0.84)	0.73 (0.60-0.86)	0.69 (0.58-0.81)	0.72 (0.61-0.84)
<b>Cut Off</b>	$\geq 24.06$			$\geq 26.20$			$\geq 24.06$		
<b>Sensitivity</b>	76.32%	39.47%	52.63%	75.86%	37.93%	51.72%	73.68%	42.11%	52.63%
<b>Specificity</b>	68.89%	100.00%	100.00%	71.88%	100.00%	100.00%	68.97%	100.00%	100.00%

[Table.]

**Design/Methods:** The study in Lima, Perú, participant's HIV+,  $\geq 18$  years with and without tuberculosis (TB). Smear, culture, and immunoassay in urine were performed. The reference was TB diagnosis by microbiological or clinical (TB treatment indication) criteria. There were 2 preanalytical process: untreated and treated urine (centrifuged, heated), then incubation with NIPAm. After wash, elution, sonication, heat and centrifugation, final eluate was obtained. This was spotted on nitrocellulose membranes, fixation and incubation with anti-esat-6 and anti-mouse IgG antibodies, revelation with C-DiGit® Blot Scanner and FluorChem R FR0001. A curve with 100, 50, 25 and 0 ng esat-6 /1ml urine was included in membranes. Density was measured using Image J software. ROC curves, sensitivity and specificity were obtained

**Results:** The result according groups were patient HIV+: ROC: 0.75 Cut point  $\geq 24.06$  ng/ml, sensitivity 76.32%, specificity 68.89%, patients  $\leq 200$  cels CD4 mm<sup>3</sup>/ml, ROC: 0.78, cut point  $\geq 26.20$  ng/ml, sensitivity 75.86%, specificity 71.88%, patients  $> 200$  cells CD4 mm<sup>3</sup>/ml, ROC 0.73, Cut point  $\geq 24.6$  CD4 mm<sup>3</sup>/ml, sensitivity 73.68%, specificity 73.68%.

**Conclusions:** The esat-6 detection assay using NIPAm was effective, higher rates in patients with  $\leq 200$  CD4 cels/mm<sup>3</sup>, test being more sensitive than smear and culture, but less specific.

### OA-05-534-21 Similarity algorithm for chest X-ray images: testing on large annotated TB patients cohort and implementation of database search service

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**Background:** In healthcare settings, content-based image retrieval systems can help clinicians query image databases using an image of interest to find similar images based on digital image features. This functionality may be especially useful for images that are linked to clinical metadata, as this extra information may inform clinical care. We evaluated strategies for chest X-ray image (CXR) similarity calculation from radiomic

features for application to the large, annotated image dataset in the NIAID TB Portals (TBP) (data.tbportals.niaid.nih.gov).

**Design/Methods:** Three strategies were used to calculate image similarity using differing image regions: (a) the whole image (b) bounding box surrounding the lungs, (c) the lung region. Lung segmentation was performed using a convolutional neural network based on the U-Net architecture. The resulting binary segmentation was morphologically eroded, removing small mask islands, so that only the lung region is retained. Features automatically extracted from these lung regions include first order statistics and various shape and intensity-based features. The features were then used in a metric learning framework. The large margin nearest neighbor metric learning algorithm was used to learn a Mahalanobis distance on the feature space based on the classification of patients' treatment outcome and drug resistance category. The resulting learned metric keeps the k-nearest neighbors in the same class while maintaining a large separation from samples belonging to other classes.

**Results:** The evaluated strategies for calculating CXR image similarity showed varying performance. The top performing algorithm has been incorporated into the TBP Radiomics Analysis Portal (rap.tbportals.niaid.nih.gov). Users utilize existing images from the TBP collection or upload external images; the system then delivers ranked similar images from the TBP database.

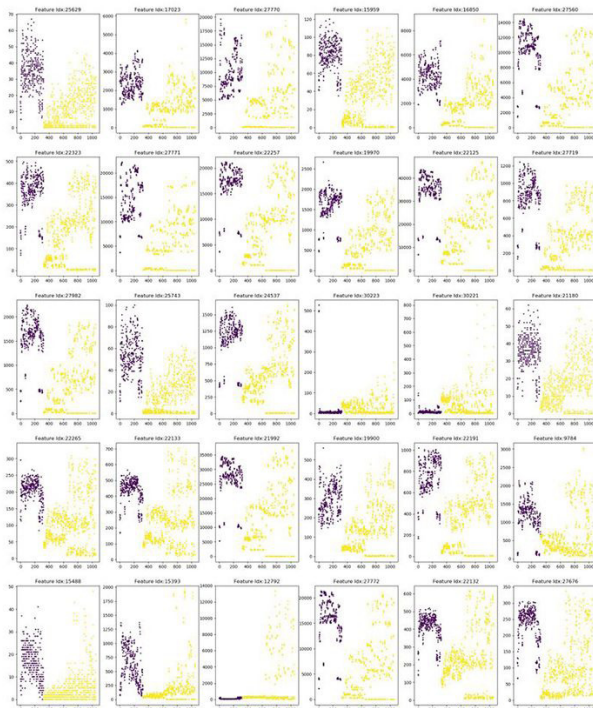
**Conclusions:** Further development is in progress and extending to CTs. With increasingly large and well-annotated clinical image datasets, image retrieval through image similarity may help physicians identify similar patient cases, providing useful context for clinical care.



**OA-05-535-21 Diagnosis of tuberculosis through exhaled volatile organic compounds using a real-time high-pressure photon ionization time-of-flight mass spectrometry**

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**Background:** Detecting tuberculosis through volatile organic compounds (VOCs) produced by Mycobacterium tuberculosis and the infected host is an attractive option due to its non-invasive nature. Here, we investigated the performance of exhaled VOCs for diagnose of tuberculosis using a real-time high-resolution high-pressure photon ionization time-of-flight mass spectrometry (HPPI-TOFMS) (register number: ChiCTR2000032733). **Design/Methods:** Pulmonary tuberculosis patients, with or without extra-pulmonary tuberculosis, who received treatment at Shenzhen Third People's Hospital were enrolled, as well as the control group selected medical staff who passed the physical examination. For tuberculosis patients, exhaled breath samples were collected before diagnosis confirmation by pathologically diagnosed, and during two weeks after anti-tuberculosis treatment. These samples were collected with customized bags and directly detected by HPPI-TOFMS, which has a resolution >4000. A deep machine learning algorithm was used to build a diagnose model based on HPPI-TOFMS data.



[Figure.]

**Results:** A total of 244 patients with tuberculosis and 131 healthy controls were included. Mass spectrum peaks with  $m/z < 500$  were detected by HPPI-TOFMS and 31666 features were extracted from each exhaled breath sample. Then 80 patients and 36 healthy controls were randomly selected to form test set and build algorithm model. Based on the algorithm model, patients who were diagnosed as tuberculosis could be discriminated from healthy control with an accuracy of 96%, sensitivity of 98% and specificity of 93%.

**Conclusions:** Exhaled VOCs detected by a real-time high-resolution HPPI-TOFMS is a promising approach for tuberculosis diagnosis.

**OA-06 Different approaches to improve treatment and care**

**OA-06-536-21 Community health worker's augment the cascade of TB detection to care in urban slums of two metro cities in India**

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**Background:** Tuberculosis Health Action Learning Initiative (THALI) funded by USAID is a person-centered initiative, supporting vulnerable urban populations to gain access to TB services. THALI trained and placed 112 Community health workers (CHWs) to support individuals with TB symptoms or disease within urban slums in two cities, Hyderabad and Bengaluru, covering a population of about 3 Million.

**Design/Methods:** CHWs visited the slums once in a fortnight. They conducted TB awareness activities. They referred individuals with TB symptoms for sputum testing to nearest public sector labs. They visited those testing TB positive, once a fortnight in the intensive phase, and once a month thereafter. They supported TB patients and families with counselling, contact screening and social scheme linkages. They complemented the shortfall in urban TB government field staff numbers and their capacity to engage with TB patients. Data on CHWs' patient referral and support activities was entered into a data-base and analyzed to examine CHWs' role in the cascade of TB care. We compared achievements between the last four months of 2016 and 2018.

**Results:** Overall, 28835 (1%) of slum population were identified as TB symptomatic and referred for diagnosis. Among the referred persons, 21547(75%) underwent testing of which 3482 (16%) were TB positive. Overall, 3454 (99%) were initiated on treatment and 2462(71%) agreed for regular followed up by CHWs.

In 2016, 58% of 1857 referred were tested, against 85% of 8417 in 2018. Overall TB notification in the two cities increased from 0.7% in 2016 to 7.2% in 2018. The treatment success rate was 84.0% among 90 in 2016 versus 93.2% among 602 in 2018.

**Conclusions:** CHWs in urban slums augment TB detection to care cascade. Their performance and TB treatment outcomes improve over time. It would be important to examine the cost per TB case detected and successfully treated.

### OA-06-537-21 Improving Isoniazid Preventive Therapy (IPT) coverage among children aged 0-14 years living with HIV through designating special clinic days, case of Kapelebyong Health Centre IV

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**Background and challenges to implementation:** TB is the leading cause of Morbidity and Mortality among People Living with HIV (PLHIV) and HIV remains the greatest risk factor for TB. TB/HIV Co-infection in children is associated with faster disease progression, severe disease forms and higher mortality compared to adults. Isoniazid Preventive Therapy (IPT) is one of the four interventions Uganda adopted to prevent TB among PLHIV, however, uptake remains low despite of its proven risk reduction of over 60% in several studies.

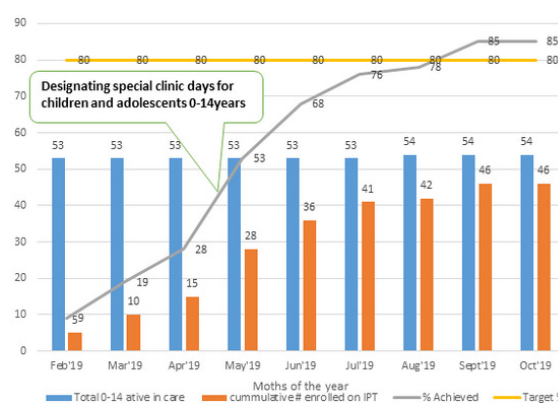
In Feb' 2019 at Kapelebyong HC 4, IPT coverage among PLHIV 0-14 was at 9% against 80% expected. This was attributed to mixing during general HIV clinic days, knowledge gap among clients/parents/guardians regarding IPT. This limited opportunities for tailored health education, screening and enrollment on IPT.

**Intervention or response:** Multidisciplinary team was set up, root cause analysis was conducted using fishbone method, Client's HIV clinic files were retrieved and reviewed, special clinic days were identified, displayed at clinical rooms and main notice board, appointment synchronization was observed. Quality Improvement (QI) concept was applied and journal opened to track

progress. Clients, parents/guardians were carefully engaged, data collection and review was done weekly and QI project was updated monthly.

**Results/Impact:** In February 2019, only 9% (5) of children and adolescents 0-14 years living with HIV were enrolled on IPT. Over a period of six months, there was significant rise in the proportion started on IPT to 85% (46) by October 2019, this is hugely linked to the invention of special clinic days which commenced in April 2019.

**Conclusions:** Designating special clinic days allows the health workers to offer comprehensive care package including IPT. Programs should prioritize development of guidelines on formulating and sustaining special clinics which offers opportunity to deal with unique challenges and help achieve optimal treatment outcomes among HIV clients.



[Figure. A graph showing cumulative coverage of IPT among 0-14 years HIV positive in Care at Kapelebyong HC 4]

### OA-06-538-21 Using market based E-pharmacies for delivering free TB drugs to patients treated in private sector, lessons learnt from a pilot in Madhya Pradesh, India

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**Background and challenges to implementation:** In India, over 50 percent of TB patients are treated in the private sector. Largely the diagnosis and treatment are of variable quality in the private sector and with no track records of patients and treatment completion. Despite, Government of India (GOI)'s commitment there is no effective mechanism for linking private sector patients

to free TB diagnosis and treatment for reducing the out of pocket expenditure, which causes non-adherence to treatment by patients.

**Intervention or response:** Madhya Pradesh state is implementing an innovative proof of concept for door step delivery of free TB drugs and linkages to free CBNAAT diagnostics for patients treated in private sector by using the market-based platform of E-pharmacies.

E-pharmacy, uses the technology platform for receiving orders for sputum collection from the door step of patients, transport to CBNAAT labs and provide reports online to the provider. Also receiving orders for free TB drugs against the valid prescription and delivers NTEP drugs to the patient's door step. The technology platform provides reminders to patients for treatment adherence and refill of drugs.

**Results/Impact:** From Jan-Mar'20, 513 sputum samples are transported from private patients and tested at NTEP-CBNAAT labs with 20% (103) positivity. There is an increase in utilization of microbiological confirmation by private providers for diagnosis by 24% (117-485) in Q1 2020 comparing 11% (36-306) in corresponding period of Q1 in 2019. TB case notification is increased to 485 (54%) in Q1 2020 from 306 in Q1 2019. The overall private provider engagement has increased to 152 in Q1 2020 (between 77-81%) from 84 in Q1 2019, 86 in Q4 2019.

**Conclusions:** Market based model of E-pharmacies can effectively be used for linking patients treated in private sector to the free TB drugs and diagnosis thus resulting into universal access to health care with minimum out of pocket expenditure.

### OA-06-539-21 The potential of mHealth to improve TB awareness and case detection in Tanzania

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**Background and challenges to implementation:** Tanzania is among the top 30 countries with a high tuberculosis (TB) burden, with an incidence of 154,000 TB cases, according to the World Health Organization's 2017 estimate. The TB treatment success rate is high at 90 percent, but one of the main challenges in controlling the epidemic is the high number of people with TB who are missing.

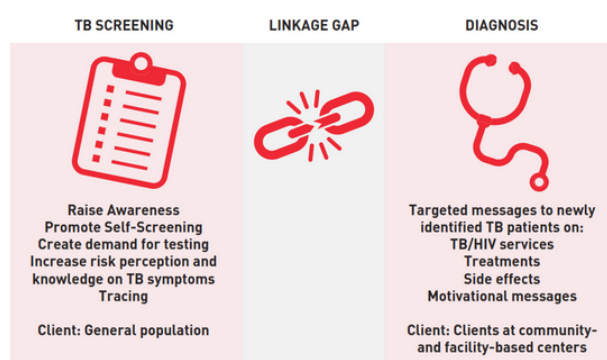
Despite the high incidence, there is a lack of TB awareness among the general population that contributes to low case notification rates. In 2017, 69,818 cases were

notified, equivalent to a 44 percent case detection rate.

**Intervention or response:** As most families in Tanzania have access to at least one mobile phone, mobile health (mHealth) technology is an opportunity to reach high numbers of people across the country in both urban and rural settings. Using mHealth technology built on existing Government infrastructure a mobile application that allows people to self-screen for TB using a basic mobile phone to increase knowledge and awareness 31 regions of Tanzania.

**Results/Impact:** Over a 7-month implementation period, 229,898 persons conducted self-screening using the Tambua app, and over a six-month period 166,758 persons self-reported as presumptive.

Of the 2,056 individuals followed up by health care workers 626 persons confirmed to have visited the diagnostic centers and 201 of them were diagnosed TB positive.



[Figure.]

**Conclusions:** mHealth has a huge potential in improving case detection rate using minimal resources if the general public is aware of the existence of those tools and encouraged to use them. The self-screening mHealth intervention improves awareness and encourage people to seek health services. Further improvements to the app may be needed such as modules for electronic referral and community activities, so that self-screening, diagnosis and treatment initiation can be linked and easily tracked.

### OA-06-540-21 Identifying subpopulations at high-risk for severe adherence challenges in the treatment of multi- and extensively drug resistant tuberculosis and HIV

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**Background:** The first new TB drug in 40 years, Bedaquiline, was introduced in South Africa in 2014 for the treatment of drug-resistant tuberculosis (DR-TB). The majority of South African DR-TB patients are HIV co-infected and receiving antiretroviral therapy (ART); adherence to each regimen is critical yet remains understudied and poorly characterized.

We used an electronic dose-monitoring device (Wisepill) to identify patients with DR-TB/HIV adherence challenges in real-time and a mixed methods approach to further characterize these challenges.

**Design/Methods:** Prospective cohort study of adult patients initiating treatment on Bedaquiline-containing regimens and Nevirapine or Lopinavir-based ART in KwaZulu-Natal, South Africa. Participants received two Wisepill devices: for Bedaquiline and ART, respectively, for 6 months. Cumulative adherence was calculated as recorded compared to expected Wisepill openings. Patients with <85% adherence to both ART and Bedaquiline were classified 'dual adherence-challenged'. Focus groups and demographic data were used to characterize adherence challenges.

**Results:** 32/198 (16.2%) enrolled DR-TB HIV patients were dual adherence-challenged and, compared to those dual-adherent, experienced higher levels of mortality at 6 months (19% vs. 6%, p=0.04). In a baseline multivariable model, only receiving a social grant predicted dual adherence-challenged patients (OR 3.8, 95% CI 1.21-11.94).

Specific challenges identified through qualitative data analysis included stigma, weak social support, alcohol/substance abuse, unstable housing and mental/behavioral health issues.

In focus group discussions, compared to dual-adherent patients, dual non-adherent patients appeared to struggle more with accepting diagnoses and prioritization of treatment among other demands.

**Conclusions:** A subpopulation of DR-TB/HIV patients experience severe adherence challenges to both Bedaquiline and ART. Electronic dose monitoring can potentially identify these patients before treatment failure or loss to follow-up. Mixed-methods reveal structural, behavioral, mental health, barriers and informs development of targeted multimodal interventions to support adherence challenged at-risk sub-populations of DR-TB HIV patients.

### OA-07 Moving away from isoniazid for TB preventive treatment

#### OA-07-542-21 Safety of high-dose rifamycin for active and latent tuberculosis: a systematic review and meta-analysis

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**Background:** There is growing interest in using rifamycins (rifampin, rifapentine, and rifabutin) at higher doses (e.g., rifampin >10 mg/kg or >600 mg daily) in tuberculosis (TB) treatment, but their safety and efficacy remain uncertain. To summarize existing evidence, we performed a systematic review and meta-analysis comparing higher-dose rifamycins (HDRs) to standard-dose rifamycins (SDRs).

**Design/Methods:** We searched Medline, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews, and clinicaltrials.gov for prospective studies comparing daily therapy with HDRs to SDRs in humans with latent or active tuberculosis.

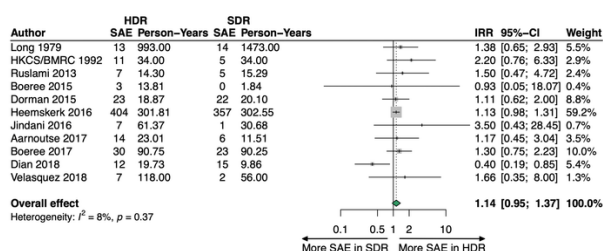
Our primary outcome was rate of serious adverse events (SAE), defined as grade 3-4 or events requiring cessation of therapy. Secondary outcomes were death, all adverse events, and SAE by organ. For active TB, we compared two-month culture conversion and relapse.

**Results:** We identified 7840 articles, of which 12 studies of 3229 people contributing 3861 person-years (PY) (HDR: 1671 people, 1752 PY; SDR: 1558 people; 2109



PY) were included in the meta-analysis. We found no difference in the incident rate ratio (IRR) of SAE between HDR and SDR (IRR = 1.14, 95% CI 0.95-1.37). There were no differences in death; culture conversion at two months; relapse; or cutaneous, hepatic, gastrointestinal, or hematologic SAE. HDR therapy was associated with greater SAE in the subgroup including all other organs (IRR = 1.20, 95% CI 1.05-1.42).

**Conclusions:** HDRs did not contribute to a significant increase in SAE. However, SAE not classically associated with rifamycins were greater with HDR therapy, suggesting there may be a role for increased surveillance for these events.



[Figure.]

### OA-07-543-21 Rifampicin maximum early bactericidal activity not reached at 50 mg/kg

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**Background:** The current standard rifampicin dose (10 mg/kg) for treating drug-susceptible tuberculosis has been shown to be suboptimal. The PanACEA HIGHRIF1 trial has recently evaluated the pharmacokinetics (PK) and early bactericidal activity (EBA) of rifampicin at 50 mg/kg after promising results for doses up to 40 mg/kg. The objectives of our work were to define if earlier developed rifampicin PK and PK-pharmacodynamics models are applicable at the 50 mg/kg dose level and if a maximum EBA could be defined at 50 mg/kg rifampicin.

**Design/Methods:** Plasma concentrations and time to liquid culture positivity (TTP) data from 95 patients from the PanACEA HIGHRIF1 trial treated with either 10, 20, 25, 30, 35, 40 or 50 mg/kg rifampicin for 7 days were included in this analysis. A previously published rifampicin population PK model and a semi-mechanistic time-to-event model developed in the dose range of 10-40 mg/kg were used to describe the PK and TTP data. Individual rifampicin AUC<sub>0-24h</sub> at day 7 was used to drive the TTP model. The models were applied to the data for

the 10-50 mg/kg dose-range with and without parameter re-estimation. Additionally, different shapes of the exposure-response relationship were evaluated.

**Results:** The previously published rifampicin population PK and TTP models described the data from the 50 mg/kg dose group well without parameter re-estimation. Re-estimation of PK and TTP model showed no difference in model parameters. As previously predicted, rifampicin 50 mg/kg group showed an increase in change from baseline TTP compared to other doses group. An E<sub>max</sub> relationship between rifampicin exposure and TTP was not significantly better than the linear relation even when the 50 mg/kg dose group data was added.

**Conclusions:** Earlier defined rifampicin population models are valid up to 50 mg/kg. Rifampicin maximum EBA is not reached at 50 mg/kg. However, use in patients might be limited by poor tolerability.

### OA-07-544-21 Treatment outcomes of people living with HIV on TB preventive therapy in Lusaka, Zambia

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**Background:** TB mortality among People Living with HIV in Zambia (PLHIV) is over 2.5 times higher than in the HIV negative population; 59% of the reported TB cases are TB/HIV co-infected. TB preventive therapy (TPT) has been proven to reduce incidence of TB among PLHIV; the reduction in TB incidence is more significant in patients who complete a course of TPT compared to those that do not. Fear of adverse outcomes among individuals initiated on TPT is one of the factors that have perpetuated limited implementation of TPT in Zambia and other settings. We present the treatment outcomes of PLHIV who were initiated on TPT in Lusaka district health facilities in Zambia.

**Design/Methods:** A retrospective analysis of IPT programme data collected between October, 2016 and March, 2020 from CDC/PEPFAR supported primary health facilities under the ACHIEVE project was done.

**Results:** A total of 54,272 (34%) PLHIV were initiated on TPT; 34,279 (63.2%) were women and 2,600 (4.8%) were children less than 15 years. Of these, 42,940 (79.1%) completed treatment, 36 (0.1%) died, 146 (0.3%) developed TB, 1,625 (3.0%) were lost to follow up and 9,525 (17.6%) were not evaluated. Completion rates in females and males were 26,985 (78.7%) and 15,955 (79.8%) respectively while completion rates were 2,141 (82.3%) and 40,799 (79.0%) in children and adults respectively.

**Conclusions:** Much as TPT initiations are still low, TPT completion rates are high across both genders and age groups. Less than 5% of people initiated on TPT had

adverse outcomes suggesting that TPT is safer than it is presumed to be. Improving uptake of TPT among PLHIV is urgently required in order to reduce the TB burden in this high-risk group.

### OA-07-545-21 A randomized controlled trial comparing two rifapentine-based short-course regimens for latent tuberculosis infection: 1HP vs. 3HP

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**Background and challenges to implementation:** Over the past decade, regimen for latent tuberculosis infection (LTBI) have evolved, from daily isoniazid for 9 months (9H) to weekly isoniazid and rifapentine for three months (3HP). 3HP regimen, however, was flawed in its systemic drug reactions (SDR). 1HP regimen, which is made up with daily 300mg isoniazid and 600mg rifapentine for 28 days, has been reported to have comparable efficacy compared with 9H and no SDRs in people living with human immunodeficiency virus.

The most relevant questions are the extrapolation of results to population other than people living with human immunodeficiency virus and direct comparison with 3HP regimen.

**Intervention or response:** This multicenter prospective randomized control trial (ClinicalTrials.gov Identifier: NCT04094012) was conducted in Taiwan. Participants, aged above 12, with LTBI diagnosed by QuantiFERON since September 2019 were randomized into 1HP and 3HP groups. Treatment outcome and safety profile, especially SDR, were investigated.

**Results/Impact:** Between September 2019 and January 2020, a total of 129 participants were randomized (1HP: 69; 3HP 60). The age in the 1HP and 3HP groups was  $52.2 \pm 22.2$  and  $53.0 \pm 19.0$ , respectively.

The completion rates were similar (90% [n=62] in 1HP vs. 82% [n=49] in 3HP,  $p=0.181$ ). Permanent discontinuation of treatment due to adverse drug reaction was observed in 7% (n=5) and 8% (n=5), respectively ( $p>0.999$ ). Among 1HP and 3HP groups, SDR developed in 2 (3%) and 9 (15%) participants, respectively ( $p=0.014$ ). However, a significant higher risk of cutaneous reaction was noted in the 1HP group than 3HP group (rash: 22% [n=15] vs. 8% [n=5],  $p=0.036$ ; itching: 28% [n=19] vs. 12% [n=7],  $p=0.025$ ). A typical cutaneous manifestation was shown in Figure 1.

**Conclusions:** The completion rate of 1HP regimen achieves 90%, similar as that of 3HP regimen, with a low risk of SDR (3%). The finding about cutaneous reaction needs further evaluation.



[Figure.]

### OA-07-546-21 Preparing for a short course treatment regimen to prevent TB: catalysing procurement and policy to scale up 3HP

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**Background and challenges to implementation:** The short course Tuberculosis Preventive Therapy (TPT) regimen known as 3HP, which combines isoniazid and rifapentine, taken only once a week for 3 months, faced obstacles to wide scale adoption, including: limited global supply of rifapentine and its inclusion on essential medicines lists (EML); limited market due to its high patient course price (\$72); and absence of 3HP in national TPT guidelines.

**Intervention or response:** Unitaid funded the Aurum Institute and its partners to implement the IMPAACT4TB project to support scale up of 3HP in 12 countries. Partners and government teams began updating TPT clinical guidelines and M&E structures, conducting

training, and determining the scale of 3HP rollout. The team participated in global 3HP price negotiations with manufacturers and discussions with donors and governments interested in purchasing 3HP. We compared commitment to national roll-out, inclusion of 3HP in guidelines, pricing, and manufacturing from February 2019 to May 2020.

**Results/Impact:** Beginning in 2019, no project country was ready to implement a national rollout of 3HP. By May 2020, 5 countries had committed to national 3HP rollouts during the year. The IMPAACT4TB countries with 3HP included in TPT guidelines increased from 6 to 11 and teams overcame import barriers for rifapentine. The cost of a patient course dropped from \$72 to \$15 and a generic manufacturer came online. In 2020, Unitaid had placed orders for 140,000+ patient courses of 3HP for project countries, with 800,000+ to be purchased by partners, including two governments, PEPFAR, PAHO, and the Global Fund, while expanding 3HP to 6 countries outside of the IMPAACT4TB project.

**Conclusions:** These findings demonstrate the pace with which the appetite for 3HP has been catalysed in these 12 countries, and globally, as many national systems are now prepared to scale the shorter course TPT regimen.

#### **OA-07-547-21 Latent tuberculosis infection testing and treatment using shortened treatment regimen for contacts and secondary school children in Do Son district, Hai Phong, Viet Nam**

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**Background and challenges to implementation:** Viet Nam ranks 11th among the 30 high Tuberculosis (TB) burdened countries with an estimated incidence of 174,000 TB patients and 13,200 TB-related deaths in 2018. In order to reach the goal of ending TB by 2030, Vietnam needs to expand proactive activities to detect and treat TB cases in the community as well as expand secondary prevention efforts to identify and treat latent TB infection (LTBI).

**Intervention or response:** As part of the TB REACH-funded SWEEP-TB project, a TB and LTBI screening campaign was conducted in Do Son district, Hai Phong province, Viet Nam in September 2019. QuantiFERON-TB Gold Plus (QFT-Plus) was used to determine LTBI status in 1,001 resident family contacts and secondary school students (age 10-14). The shortened 3RH regimen was used to treat eligible persons with LTBI. Local

commune health officers and community health workers supported the provision of LTBI treatment, which included weekly adverse event monitoring.

**Results/Impact:** The LTBI rate was 19.1% (191/1,001) and increased with age. In children <15 years the rate was 6.3% (42/653). In participants aged 15-54 and ≥55 years the rates were 35.9% (86/239) and 57.8% (63/109), respectively. LTBI prevalence in household contacts was 38.6% (68/176) compared to 14.9% (123/825) in all others. Of the 191 people with LTBI, 157 (82.2%) were eligible for latent TB treatment and 77.1% (121/157) were enrolled for treatment. Nobody experienced a serious adverse event. The rate of adverse events was 17.4% (21/121), most commonly consisting of fatigues (10.7%) and appetite loss (8.3%). The overall treatment completion rate was 83.5%.

**Conclusions:** LTBI treatment with 3HR was well-tolerated and yielded high completion rates. There is a need to expand screening and early LTBI treatment. Shortened regimen may help to increase uptake and adherence.

#### **OA-07-548-21 Impact of age on completion rate and systemic drug reaction of rifapentine-based weekly therapy for latent tuberculosis infection**

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**Background:** Weekly rifapentine and isoniazid (3HP) has become an attractive regimen for latent tuberculosis infection (LTBI) treatment given its short course and high completion rate. A comprehensive assessment of treatment outcome of 3HP covering all-aged population is essential for widespread use.

**Design/Methods:** Participants receiving 3HP for LTBI diagnosed by QuantiFERON were retrieved from 1 randomized controlled trial and 2 prospective observational studies conducted from September 2014 to December 2019 and stratified into 3 age groups (elder group: ≥65; middle-age group: 35 ~ 65; younger group: ≤35). The impact of age on treatment outcome were investigated, with a special emphasis on discontinuation of 3HP and development of systemic drug reaction (SDR).

**Results:** Among 579 participants receiving ≥1 dose of 3HP, 481 (83.1%) completed treatment, and 362 (62.5%) experienced ≥1 adverse event (AE). The num-

ber of subjects in younger, middle-age, and elder groups was 165, 280, and 134, respectively. The younger group had a highest rate of treatment completion (94.5%) and AEs (62.8%), whereas the rates were lowest in the elder group (73.9% and 41.4%, respectively). A higher proportion of subjects (7.5%) in the elder group experienced severe AEs (Grade  $\geq 3$ ). The overall risk of SDR was 11.0%, and was highest (16.8%) in the middle-age group. Multivariate analysis revealed that middle-age group had 3.65-folds higher risk of developing SDR than elder group ( $p < 0.001$ ), and the finding was consistently observed in great majority clinical settings. The risk of SDR was similar in the elder and younger groups. Compare to elder group, the younger group had a slightly lower, but not significant risk of treatment discontinuation.

**Conclusions:** Under proper medical support and programmatic follow-up, the completion rate of 3HP is great even for the elders, and caution should be given for middle-age population.

## OA-09 What person-centred care really means

### OA-09-550-21 Using the Patient Pathway Analysis method to align care seeking and service delivery in development of a person-centered National Strategic Plan

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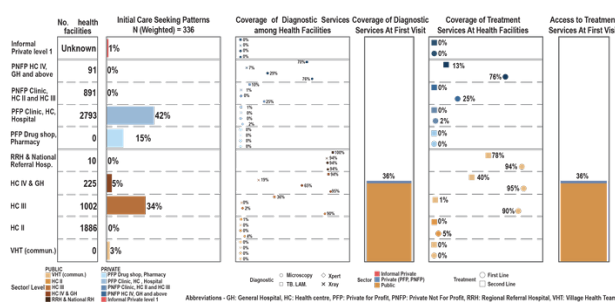
**Background and challenges to implementation:** Patient-centered interventions comprise pillar one of the World Health Organization's End Tuberculosis (TB) strategy. Using findings that revealed almost 50% of cases were missed, Uganda's national strategic plan recommended assessment of missing cases in all sectors providing health services and patient-centered models of care to improve case finding and service delivery coverage.

**Intervention or response:** As part of strategic plan data consolidation, a patient pathway analysis (PPA) was carried out to assess alignment between initial care-seeking and service delivery in the public and private sector. Care seeking behavior from the demographic and health survey was mapped against service availability from the health facility master list and program

inventories. Mapping was categorized by sector (public, private not for profit, private for profit and informal private) and level (village health team, health centre (HC) II, III, IV; general, regional and national referral hospitals) using the online PPA platform.

**Results/Impact:** Uganda national level PPA. 58% of people with symptoms relating to TB initially sought care from the private sector yet only 2% of private facilities had capacity to diagnose TB. In contrast, 34% of the surveyed population sought care from lower level public facilities, with 90% (microscopy) and 2% (GeneXpert) capacity to diagnose TB. Whereas 95% of higher-level facilities could diagnose TB, only 5% of the population initially sought care from these.

Overall, only 36% of the population had access to diagnostic and treatment services at first visit, mostly in the public sector.



[Figure.]

**Conclusions:** Significant misalignment between initial care seeking and TB service delivery using evidence informed the focus for the new national strategic plan: Engaging the private sector, creating awareness and strengthening of screening and diagnostic access at lower health units.

We recommend the PPA for countries to evaluate gaps in alignment of care seeking and service delivery as they develop person centered strategic plans.



**OA-09-551-21 A 360° view of TB-related stigma in Uganda: findings from a mixed-methods study involving perceptions from patients, providers, and communities**

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**Background:** Tuberculosis (TB)-related stigma is complex and challenging, impacting the full spectrum of TB care and prevention services from care-seeking in programs that use stigmatizing language (e.g., “suspects”), notification systems that often lack privacy, and treatment guidance that requires some degree of isolation by TB patients from families and communities. Such practices fuel stigma towards patients at multiple levels.

**Design/Methods:** To understand the scope of stigma in Uganda, a mixed-method study was conducted as part of MEASURE Evaluation’s Uganda Quality of TB Services Assessment from Oct–Nov 2019. The study included a survey of 357 TB service providers and 501 TB patients as well as 8 focus group discussions with community members. Data was analyzed, triangulated, and synthesized to show results from each perspective.

**Results:** Patients experienced stigma from multiple levels/sources: community, healthworkers, family, and self. They perceived most stigma from the community and their own self-stigmatized attitudes, with low levels of stigma coming from healthworkers. Healthworkers expressed higher levels of stigma towards TB patients than towards healthworkers with TB (see stigma scores in Table 1).

Domain	Mean Score (raw)	Score Range	Adjusted Score (%)	Adjusted Score* (on a scale of 1 to 5)
Facility/health worker (n=500)	15.5	8-40	38.8	1.9
Community (n=481)	11.4	4-20	57.0	2.85
Family/friends (n=332)	6.9	3-15	46.0	2.3
Self (n=498)	32	12-60	53.3	2.67

\*NOTE: Higher score indicates higher levels of perceived stigma

[Table 1. Stigma scores based on TB patients perceptions across four domains]

Community members expressed mixed understanding of TB and held multiple misconceptions, describing TB with biomedical phrases and myths about TB etiology that illustrated negative attitudes and prejudices. However, not all actions termed stigma at the community level were found to have negative effects. Community members expressed a moral obligation to care for people with TB, and the idea of isolating them was seen as not socially or culturally acceptable.

**Conclusions:** Patients experience stigma coming from multiple sources. Most perceived stigma came from the community, but many patients also reported being stigmatized by the healthworkers. Because stigma can have a major impact on preventive measures and treatment outcomes, a deeper understanding of stigma is needed to address its negative effects and to reinforce positive actions.

**OA-09-552-21 Support for integrating tuberculosis preventive treatment (TPT) into community antiretroviral refill groups (CARGs) among people on antiretroviral treatment (ART) in Zimbabwe**

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**Background:** Although tuberculosis (TB) is a leading cause of death for people living with HIV (PLHIV) in Zimbabwe, only 11% of PLHIV newly enrolled in HIV care received TB preventive treatment (TPT) in 2017. Zimbabwe’s Ministry of Health and Child Care plans to expand TPT access to PLHIV doing well on antiretroviral therapy (ART) and enrolled in community-based group treatment models, such as Community ART Refill Groups (CARGs).

**Design/Methods:** We conducted 16 focus group discussions (FGD) with 136 adults in CARGs to explore attitudes about integrating TPT into the model. 8/16 FGD included PLHIV who had previously received TPT. Participants were recruited from 4 urban and 3 rural public-sector health facilities. FGD were conducted in Shona, transcribed, translated into English and analyzed using Dedoose™ to support thematic analysis.

**Results:** Participants had been on ART for a median of 8 years (IQR 6,11); half had been in CARGs for > 2 years. 68% were women; median age=46.5 years (IQR 42,54; range=12). Most supported provision of TPT via CARGs, preferring models that included multi-month dispensing (MMD) of TPT that would enable them to remain in CARGs vs. models that required leaving CARGs temporarily while on TPT. Irrespective of previous TPT experience, participants were comfortable with being monitored by their lay CARG leaders, and highlighted adherence support, information-sharing, close monitoring, and cost and time-savings as key advantages. “When we are as a group, we will encourage each other to endure.” Concerns included the increased workload for CARG leaders, the potential for medication stockouts related to MMD, and perceived lack of medical monitoring.

**Conclusions:** PLHIV in CARGs were confident that TPT could be integrated into this community-based model, and felt that education, psychosocial support, adherence monitoring and support, and screening for side effects could be provided effectively in this setting.

#### OA-09-553-21 Integrating mental health services into tuberculosis care: Gujarat, India

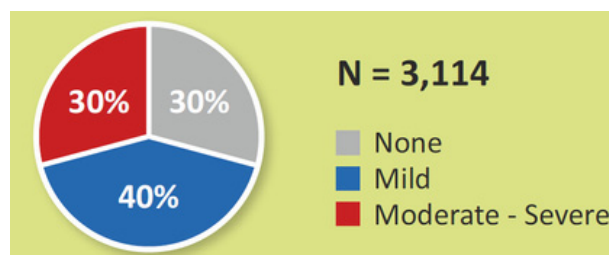
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**Background and challenges to implementation:** The TB–Depression syndemic is the product of complex relationships between social, biological, and behavioral factors. TB-related stigma can lead to internalized feelings of shame, guilt, and social isolation. People who are depressed are more likely to use negative coping strategies such as alcohol and drug abuse, resulting in delays in seeking anti-TB treatment, reinfection, and drug resistance.

**Intervention or response:** Mental health services were implemented in the districts of Ahmedabad and Surat, Gujarat. The PHQ-9 screening tool for depression was adapted for non-specialist management and TB workflows. TB patients were screened for depression during the first home visit for TB counseling. TB health workers were trained on psychotherapeutic interventions that used interpersonal psychotherapy and behavioral activation strategies.

Patients were administered four to six sessions during intensive phase of TB treatment. The screening tool was administered after each session to monitor changes in depression symptoms. Referrals to specialized care were made if patient did not show improvement or expressed symptoms of severe illness.

**Results/Impact:** 3,114 TB patients over a period of 6 months were screened for depression. 30% had no symptoms; 40% exhibited mild symptoms; and 30% exhibited moderate to severe symptoms of depression. 3.3% of patients expressed thoughts of injuring themselves. Higher prevalence of moderate-severe depression was identified among retreatment cases (37%), drug-resistant TB cases (52%), tribal groups (45%), and alcohol users (53%). Of patients enrolled in intervention, 54% of patients experienced a reduction in depression symptoms from “moderate-severe” to mild or none by end of session 2 (n=211), 65% by session 3 (n=110), and 72% by session 4 (n= 61).



[Figure 1: Prevalence of Probable Depression among TB Patients.]

**Conclusions:** High prevalence of depression among TB patients indicates that routine mental health screening is required and feasible. Psychotherapeutic counseling delivered by health workers can improve depression symptoms and integrate patient-centric metrics of care.

#### OA-09-554-21 Journey patterns and models of care observed in patients receiving drug-resistant tuberculosis treatment in South Africa

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**Background:** It has been seven years since South Africa made a call to decentralise DR-TB care. Little is known about which journey patterns and models of care have

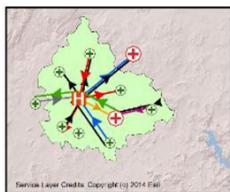
emerged. The aim of this analysis is to use spatio-temporal mapping of patient care pathways, to describe these diverse patterns ranging from highly centralised to highly decentralised and use these to provide structure to illustrate existing models of care.

**Design/Methods:** A retrospective observational study was conducted in 13 high burden urban and rural districts within three purposively sampled provinces. Patients with DR-TB were sampled from routine state laboratory records from July-Sept 2016. Care pathways for 194 randomly selected patients were reconstructed and calculated, through incorporation of laboratory records and patient folder reviews.

**Results:** Within the patient cohort, 62% (n=121) were urban residents, 69% (n=134) were HIV-positive and 63% (n=122) had previous TB.

Five dominant geospatial movement patterns emerged, based on the type and number of health care facilities involved in initial and follow-up patient care. The patterns were distinguishable from an aerial perspective and named according to the composite pathway appearance. Patterns varied in average hospital stays (0-103 days), patient distance traveled (12- 208km), retention in care at 6 months (60-100%) and favorable treatment status at 2 years (50- 85%).

The most commonly found pattern was termed ‘hub and spoke’ (n=72) due to its reliance on a pivotal decentralized DR-TB facility, with the ‘spokes’ illustrating the links to the referral and follow-up primary health care facilities.



[Figure 1.]

Two patterns (n=28) were observed which offered a high degree of decentralization and relied upon primary health care facilities alone, for the duration of treatment.

**Conclusions:** Individual patient pathway pattern analysis can assist health services to understand care models in their setting, and plan the transition towards increasingly decentralized care options, in order to meet the needs of DR-TB patients.

### OA-09-555-21 Implementation of a supportive care package to strengthen drug-resistant tuberculosis patients’ adherence to treatment in Xi’an, China

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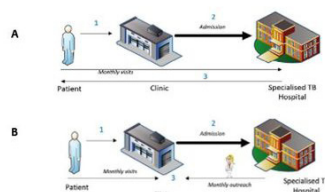
**Background and challenges to implementation:** Treatment of multidrug-resistant tuberculosis (MDR-TB) is complicated and challenging due to the length of treatment, severity of disease, limited patient understanding of complicated regimens, social stigma, and huge financial burden.

In China, the treatment success rate (TSR) for the 2016 MDR-TB cohort was only 52%. Xi’an Chest Hospital (XCH), a provincial-level MDR-TB care facility in Shaanxi Province, Western China, implemented a comprehensive supportive care package for MDR-TB patients from Feb 2019 to improve outcomes.

**Intervention or response:** The comprehensive supportive care package included: an individualized care plan developed with and for patients; face-to-face and online education and counseling for patients and their families provided by nurse counsellors and peer educators; data-driven MDR-TB case management; and community-based care for ambulatory patients. XCH established working groups internally, and with local CDC and communities, to address emerging challenges and facilitate coordination to implement the package.

**Results/Impact:** Chi-square test was used to compare 176 patients diagnosed between March and Aug 2019 with a historical, pre-intervention group of 155 patients diagnosed in the same period in 2018. By the end of January 2020, the 2019 cohort performed better in terms of treatment enrollment (96% vs.89.7%, p=0.023), treatment retention for at least six months (85.2% vs. 73.3%, p=0.000) and LTFU (5.3% vs. 19.4%, p=0.000) as of January 2019. Patients in the 2019 cohort also completed 95.8% (542/566) of the required treatment monitoring visits scheduled from March to Aug 2019, a 16.2% increase from 82.4% (347/421) for the 2018 cohort.

**Conclusions:** Preliminary data suggest that the supportive care package effectively strengthened patient retention in MDR-TB care, contributed significantly to reducing LTFU, and strengthened treatment adherence. Expansion of this package to other sites in Shaanxi province, western China could increase successful treatment outcomes for many individuals with MDR-TB.



## E-POSTER SESSION (EP)

### EP01 Resisting the resistance

#### EP01-100-21 Pharmacokinetics of anti-tuberculosis drugs in multidrug resistant tuberculosis patients in India

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**Background:** A pharmacokinetic (PK) study of drugs used to treat MDR TB, namely levofloxacin (LFX), ethionamide (ETH), cycloserine (CS), pyrazinamide (PZA), moxifloxacin (MFX) and isoniazid (INH) was undertaken in adult MDR TB patients treated according to the prevailing guidelines in India. Factors influencing drug PK and end-of-intensive phase (IP) culture conversion status were analysed.

**Design/Methods:** We recruited 350 MDR TB patients receiving anti-TB treatment (ATT) in the Indian Government programme in south India. At steady state, serial blood samples were collected, after supervised drug administration. Certain PK variables were calculated based on non-compartmental analysis. Status at end of IP was noted from the programme records.

**Results:** Of the 303 patients for whom end-of-IP status was known, 214 were culture negative, while 45 patients were either culture positive or required change of regimen or had died before completion of IP. Patients who had defaulted treatment (n = 44) were excluded from analysis. The median C<sub>max</sub> (2.9 vs 2.0 µg/ml; p = 0.005) and AUC<sub>0-12</sub> (17.0 vs 12.2 µg/ml.h; p = 0.002) of ETH were significantly higher in patients who were culture negative at end of IP than those patients who remained culture positive/required regimen change/died. In multivariate logistic regression analysis, AUC<sub>0-12</sub> of ETH significantly influenced end-of-IP status (aOR - 1.065; 95% CI: 1.001 - 1.134; p = 0.047).

**Conclusions:** This is the first report describing the PK of second-line anti-TB drugs in MDR TB patients in India. The drug doses used currently in the programme produced optimal drug concentrations in majority of patients. In multivariate regression analysis, we dem-

onstrated drug doses to have a significant influence on the drug concentrations of ETH, PZA, MFX and INH, and there was a direct relationship. ETH played a major role in the MDR TB combination regimen and was a key determinant at the end-of-IP culture conversion status.

#### EP01-101-21 Multidrug-resistant tuberculosis and its determinants of health service, community and social context in the state of São Paulo, Brazil

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**Background:** Multidrug-resistant tuberculosis (MDR-TB) remains a serious public health problem worldwide. Social Determinants of Health (DSS) are recognized as important risk factors related to their occurrence, and their knowledge can facilitate the prevention and control of the disease. Thus, we seek to identify the DSS associated with the occurrence of MDR-TB.

**Design/Methods:** We conducted an ecological study with all MDR-TB cases diagnosed between 2006 and 2016 in the state of São Paulo, Brazil. We considered the 645 municipalities as the unit of analysis. From the case count in the period, the Generalized additive models for location, scale and shape (GAMLSS) and the Waring distribution were considered as modeling structures to analyze the DSS related to the disease.

Explanatory variable	Coefficient	P Value
Demographic density	0.002	0.02*
Percentage of inhabitants with access to sewage	-0.022	0.03*
Average public expenditure in the health sector (per thousand inhabitants)	-0.001	0.01*
Municipality with prison unit	0.577	0.02*
Degree of urbanization	0.038	<0.01*
Proportion of men in the population	0.018	<0.01*
Total inhabitants	0.001	<0.01*
Number of sputum cultures not performed in diagnosed tuberculosis cases	-0.006	<0.01*
Average medical professionals (per thousand inhabitants)	-0.556	0.04*

[Table 1.]

**Results:** 867 cases of MDR-TB were diagnosed. The results of the regression analyzes (Table 1) show a greater occurrence of MDR-TB in municipalities with the presence of prison units ( $\beta=0.577$ ;  $p=0.02$ ) and with greater

demographic densities ( $\beta=0.002$ ;  $p=0.02$ ), degree urbanization ( $\beta=0.038$ ;  $p<0.01$ ), total number of inhabitants ( $\beta=0.001$ ;  $p<0.01$ ) and proportion of men in the population ( $\beta=0.018$ ;  $p<0.01$ ). Municipalities with population who have less access to sanitation had a higher incidence of the disease ( $\beta=-0.022$ ;  $p=0.03$ ). In the health system variables, it was found that public investment in health ( $\beta=-0.001$ ;  $p=0.01$ ) and the availability of medical professionals ( $\beta=-0.556$ ;  $p=0.04$ ), had a significant impact on the case scenario. Failure to perform a culture test among tuberculosis cases resulted in a lower number of MDR-TB cases diagnosed in the municipalities ( $\beta=-0.006$ ;  $p<0.01$ ).

**Conclusions:** The knowledge of DSS related to MDR-TB contributes to the control and management of these cases. However, the modification of these determinants is directly related to the elaboration of public policies that strengthen the health system and allow access to services and goods in regions most in need.

### EP01-102-21 Decentralized care for rifampicin resistant tuberculosis in Western Cape, South Africa: a laboratory cohort study

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**Background:** In 2011, South Africa implemented a policy to decentralize and deinstitutionalize rifampicin resistant tuberculosis (RR-TB) care to reduce the hospitalization burden on patients and allow treatment closer to home. We assessed care patterns after policy implementation in Western Cape, where care moved from six specialized TB hospitals to 406 local facilities.

**Design/Methods:** We analyzed laboratory results from the National Health Laboratory Service at Greenpoint, Western Cape from patients diagnosed with RR-TB, January 2012-July 2014. Expecting that the policy would change patients' care patterns, we calculated (a) the percentage of patients with RR-TB providing a sample at any of the six TB hospitals and (b) hospital stay length for those moving from a TB hospital to local facilities in the first year after diagnosis. We assessed temporal changes in these measures with linear regression. We stratified by Cape Town versus other districts, where the impact might be greater given the low number of TB hospitals delivering RR-TB treatment.

**Results:** Of the 2878 patients with RR-TB, 1878 (65%) were diagnosed in Cape Town and 1000 (35%) outside Cape Town. In the first year after diagnosis, 545 (29%) of those in Cape Town and 683 (68%) of those outside Cape Town were hospitalized in a TB hospital. The percentage of patients in Cape Town in a TB hospital decreased by 1%/quarter ( $p=0.017$ ), but not significantly outside Cape Town.

Similarly, for Cape Town patients that moved out of a TB hospital, the first TB hospital stay length decreased by 4.2 days/quarter ( $p=0.076$ ) but stayed constant over time for those outside Cape Town.

**Conclusions:** From 2012-2014, RR-TB care decentralization was implemented faster inside than outside Cape Town, likely due to challenges in rural areas. Locations outside Cape Town may need more policy implementation support, potentially offering insight into implementation elsewhere in South Africa.

### EP01-103-21 Effectiveness, safety and feasibility of 9-month treatment regimen (9MTR) for rifampin-resistant TB in the Philippines

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**Background:** The Philippines has a large burden of drug-resistant TB (DR-TB). One of key challenges in programmatic management of DR-TB (PMDT) is the high rate of loss to follow-up (38% in 2010 cohort). Urgent need for a shorter, more tolerable and less expensive treatment regimen exists.

**Design/Methods:** A prospective single-arm study evaluated 10 tertiary hospitals (8 government and 2 non-government) implementing PMDT under the satellite treatment centers (STCs) model. All eligible consenting adult patients with rifampin-resistant TB were enrolled and received the standardized 9MTR (included injectables) with 12 months follow-up after completion of therapy.

**Results:** A total of 329 patients were enrolled during 07/2015-12/2016. At 6 months post-enrollment 256/329 (78%) were sputum culture negative. End-of-treatment success rate was 74% (224 [68%] were cured, 20 [6%] completed treatment), 3% (n=10) died, 12% (n=41) were lost to follow up, 10% (n=33) were withdrawn from treatment (due to participant refusal, adverse event

[AE] including pregnancy, or acquired drug resistance) and 0.3% (n=1) had treatment failure. At 12 months after 9MTR completion 198/245 evaluated (81%) were culture negative and for 46/245 (19%) cultures were not done. One participant (of 245) developed relapse (with fluoroquinolone resistance). A total 210 AEs of grade  $\geq 3$  were reported. When WHO recommended programmatic use of 9MTR in 2016, the Philippines was able to scale it up quickly to cover 80% of all DR-TB treatments in the country by 2017.

**Conclusions:** 9MTR had a high treatment success rate with a favorable safety profile. Loss to follow-up was much reduced, but is still a challenge. The introduction of 9MTR via operational research had a major impact on building national capacity and infrastructure for programmatic adoption of the new regimen. Ten centers throughout the country received training and experience, diagnostic pathways were created, and capacity for drug safety monitoring and management was built.

### EP01-104-21 Characterising multidrug-resistant tuberculosis transmission in rural KwaZulu-Natal: a prospective cohort study

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**Background:** South Africa has one of the highest tuberculosis (TB) burdens globally, with KwaZulu-Natal among the worst affected regions. Increasing drug resistance, driven by transmission, seriously threatens recent progress in curbing this epidemic. Understanding drivers of transmission is crucial to inform targeted interventions. Whole genome sequencing is an increasingly central molecular genetic tool in characterising transmission patterns of *Mycobacterium tuberculosis* (*Mtb*).

**Design/Methods:** 129 *Mtb* isolates from 202 adults diagnosed with multidrug-resistant TB between January 2016 and February 2019 in Hlabisa subdistrict, Kwa-

Zulu-Natal, South Africa, underwent whole genome sequencing. Genomic transmission clusters of cases were identified based on the number of differing single nucleotide polymorphisms (SNPs), with clusters defined as  $\leq 10$  SNPs. The relative frequencies of 15 demographic characteristics and TB lineage were compared between clustered and non-clustered cases. *rpoB* mutations were compared between samples in each genomic cluster.

**Results:** Nine genomic clusters were identified with cluster size ranging from two to six. 31/129 (24.0%) samples clustered with at least one other isolate. No significant associations were found between lineage or the presence of any of the 15 demographic variables and being part of a transmission cluster (Table).

Variable:	n clustered /N(%)	Crude OR (95% CI)	P-value	Variable:	n clustered /N(%)	Crude OR (95% CI)	P-value	Variable:	n clustered /N(%)	Crude OR (95% CI)	P-value
HIV status:			P=0.31	Sex:			P=0.99	Lineage:			P=0.65
HIV negative	3 / 18 (16.7%)	1		Male	18 / 75 (24.0%)	1		1	0 / 5 (0.0%)	-	
HIV positive not on ART	11 / 32 (34.4%)	2.62 (0.62 -11.04)		Female	13 / 54 (24.1%)	1.00 (0.44 -2.28)		2	12 / 51 (23.5%)	1	
HIV positive on ART	17 / 75 (22.7%)	1.47 (0.38 -5.67)		Previous TB treatment:			P=0.64	3	0 / 3 (0.0%)	-	
Age:			P=0.95	No	16 / 62 (25.8%)	1		4	19 / 70 (27.1%)	1.21 (0.53 -2.79)	
<30	7 / 30 (23.3%)	1		Yes	14 / 63 (22.2%)	0.82 (0.36 -1.87)		Previous inpatient in hospital:			P=0.32
30-39	13 / 49 (26.5%)	1.19 (0.41 -3.42)		Recently moved municipality:			P=0.13	No	19 / 89 (21.3%)	1	
40-49	7 / 30 (23.3%)	1.00 (0.30 -3.31)		No	23 / 106 (21.7%)	1		Yes	11 / 37 (29.7%)	1.56 (0.65 -3.71)	
50+	4 / 20 (20.0%)	0.82 (0.21 -3.28)		Yes	7 / 18 (38.9%)	2.30 (0.80 -6.59)					

[Table]

Fewer than half of patients (63/129 [49%]) had been previously treated for TB, and all except one cluster shared the same *rpoB* mutation indicating that drug resistance was predominantly transmitted rather than acquired.

**Conclusions:** This study provides further evidence that transmission, rather than acquisition, is the key driver of increasing TB drug resistance – a salient finding in an era where drug resistance is a major threat to efforts to end TB.

### EP01-105-21 Effectiveness and safety of use of Bedaquiline (BDQ) and Delamanid (DLM) in combination for Drug Resistant Extrapulmonary TB (EPTB) in Mumbai, India

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**Background:** Diagnosis of EPTB is difficult due to variable clinical presentation and need for invasive procedures to secure sample. We aimed to evaluate effectiveness and safety of combination of bedaquiline and delamanid among EPTB patients.

**Design/Methods:** This is a descriptive study of routinely collected programme data in EPTB patients initiated from April 2016 to October 2019. DRTB was confirmed on culture and Drug susceptibility testing (DST) or confirmed on radiology/histopathology with failure on prior TB treatment. Patients were treated with individualized DST based regimens. Response to treatment was monitored clinically and radiologically. Grade three and four severe adverse events (SAE) of clinical importance are reported.

**Results:** A total of 17 drug resistant EPTB patients were initiated on BDQ and DLM combination regimen. Females constituted 12 (70.5%) and median age was 23 years (IQR=9). Fourteen (82%) had previous history of TB. 41% (7/17) were diagnosed XDR TB, 47% (8/17) pre XDR and two patients were radiologically confirmed. Sites of involvement were lymph node 53% (9/17), central nervous system 17.6% (3/17), spine 17.6% (3/17), pleural effusion 5.8% (1/17) and cold abscesses 5.8% (1/17). In patients with final treatment outcomes (N=11), eight completed treatment (72.7%), two died and one was lost to follow-up (LTFU). For treatment completion, the median duration of treatment was 21 months (IQR=6). Six patients on treatment are improving. One patient reported three episodes of Qtc prolongation (>500msec), attributable to moxifloxacin. Two patients (11.7%) reported hepatitis, three episodes in total. Ten patients (58.8%) had at least one SAE. BDQ and DLM were not stopped permanently due to severe adverse events.

**Conclusions:** Treatment outcomes among patients with drug-resistant EPTB, using the combination of bedaquiline and delamanid under programmatic conditions in Mumbai, were encouraging. Our study data contribute to the evidence-base for expanding access to new drugs for drug resistant EPTB patients.

### EP01-106-21 Eliciting patient preferences for different attributes of a community-based model for management of multi-drug resistant tuberculosis in Uganda: a discrete choice experiment

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**Background:** Community-based directly observed therapy (CB-DOT) results in better treatment outcomes for both drug susceptible and multi-drug resistant tuberculosis (MDR-TB) than health facility-based DOT. The advent of all-oral regimens for the management of MDR-TB makes the implementation of CB-DOT a possibility for this group of patients. We set out to determine patient preferences for different attributes of a CB-DOT model for the management of MDR-TB in Uganda.

**Design/Methods:** We conducted a cross sectional study at five tertiary referral hospitals. We used a discrete choice experiment with three different attributes of community-based care (provider type, location of care, and type of support) combined into eight choice sets, each with two options and an opt-out choice. We collected data using pictorial questionnaires. We fitted a mixed logit choice model to determine patient preferences for different attributes of community-based care.

**Results:** From December 2019 to January 2020, 103 participants were interviewed. The majority (58.3%) were male; 61.2% were HIV negative; and, median age was 37 (IQR 30-47) years. Two thirds (65.1%) earned less than \$1/day. Study participants preferred at least one of the CB-DOT models of care to none (current standard of care). The most preferred model consisted of a community health worker giving DOT at home and travel vouchers to enable attendance at monthly clinic follow-up visits. HIV+ve patients had a significantly higher preference for treatment delivered at home (p-value=0.04). Patients on MDR-TB treatment for ≥6 months had a significantly higher preference for treatment delivered by a community health care worker or expert client (p-value = 0.02) compared to a family member.

**Conclusions:** Patients with MDR-TB prefer to be supported to take their medicine at home by a member of their community. The effectiveness of this model of care should be further evaluated and considered to guide development of an effective CB-DOT program for TB care.



### EP01-107-21 Treatment of multidrug-resistant tuberculosis with modified shorter all-oral treatment regimen: Belarus operational research study

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**Background:** Recently WHO recommended that modified shorter all-oral treatment regimens (mSTR) for multidrug-resistant tuberculosis (MDR-TB) should be considered by countries under operational research conditions.

**Design/Methods:** In October 2018 Belarus started operational research study on the use of mSTR for MDR-TB patients. Thirty-nine-week regimen with Lvx, Bdq, Lnz, Cfz and Cs was selected. To be included patients should have laboratory confirmed TB with initial resistance to at least R. Exclusion criteria are: resistance to or previous treatment with any drug of the regimen; QTcF interval longer than 500 msec; ALT/AST more than 5 times higher than upper limits.

**Results:** By 1st May 2020 415 patients were included in the study. Of them 114 had final treatment outcomes: the median age was 45 years; 81% males; with co-morbidity: HIV - 6%, HCV - 7%, DM - 4%, Harmful use of alcohol - 23%. The following final treatment outcomes were recorded: treatment success: 102 (89%); lost to follow up: 2 (2%); treatment failure: 4 (4%); death: 6 (5%). All deaths were not due to TB or medication. The adverse events were mild and did not prompt the treatment to be stopped.

**Conclusions:** Preliminary results on the use of mSTR for MDR-TB under operational research conditions in Belarus are encouraging. We hope our data as a part of the global database will be able to create the evidence whether or not to further expand mSTR for MDR-TB to programmatic level.

### EP01-108-21 Patient's perspective on drug resistant-TB medication: does it matter? Putting research into action to develop information, education, and communication material

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**Background:** To identify the enabling factors and challenges of drug resistant-TB (DR-TB) treatment success as a basis for developing DR-TB information, education, and communication (IEC) material.

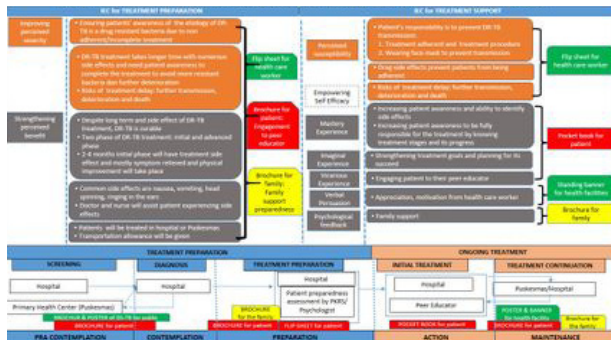
**Design/Methods:** A qualitative study was done in six health facilities within three districts in Indonesia to determine perceptions and experiences on DR-TB treatment. A total of 41 participants consisting of TB patients, patients' families, health care workers, psychologists, health promotion officers, and peer educators were selected purposively. Simple content analysis framework adjusted to the health belief model (HBM) domain was done.

**Results:** Challenges were drawn from low perceived susceptibility (low awareness of the risk of developing DR-TB), perceived severity (physical, psychological, and economic burdens) and perceived barriers (debilitating of treatment side effects and treatment duration). Enabling factors (perceived benefits) were a physical improvement, transportation allowance, supplementary feeding, internal motivation (fear of death due to DR-TB and fear of transmitting the disease to the family) and external motivation (peer support). These became the cues to action for treatment success but the most important was a guarantee that the disease can be cured and motivation from significant others, health care workers, and other DR-TB patients. Self-efficacy played an important role in treatment continuation as it's directly related to cues to action, patient's knowledge, mastery experience in managing medication side effect, vicarious experience (interaction with ex Dr-TB patients), verbal persuasion, emotional and psychological condition (Fig. 1).

**Conclusions:** IEC material of DR-TB medication shall focus on raising awareness of developing DR-TB and its debilitating impact. Delivering DR-TB treatment benefits and allowance at the earliest time and addressing its barriers and solutions would be essentials. Assessing patients' readiness for starting treatment, counseling, and



building patients' self-confidence is mandatory. Education for DR-TB patients shall be started at each phase of screening, diagnosis, treatment preparation, ongoing treatment, and its continuation (Fig. 1).



[Figure 1. DR-TB IEC material based on Health Belief Model and Transtheoretical Model]

## EP01-109-21 The role of clinical healthcare champions in driving drug-resistant tuberculosis policy implementation in South Africa

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**Background and challenges to implementation:** Clinical champions are dynamic individuals with interest and commitment to adopt and support a particular cause in healthcare. In South Africa, champions have emerged as a driving force behind the implementation of decentralised and deinstitutionalised management of drug-resistant tuberculosis (DR-TB). However, little

is known about the roles of champions and factors influencing their strategies. Using a realist approach, this study explored the typology and roles of champions in the decentralisation of DR-TB management, strategies that champions used to implement policy and the contextual factors that enabled or acted as barriers to their agency.

**Intervention or response:** The realist analysis was based on 34 in-depth and nine semi-structured interviews with DR-TB clinicians, healthcare workers and coordinators to explore their experiences of implementing a policy for decentralised care of DR-TB in South Africa. A thematic framework was created, and data relating to central themes were extracted. Data were organised through the lens of a realist approach into contextual factors, mechanisms and outcomes.

**Results/Impact:** Two types of clinical champions, disease-centred and patient-centred, emerged in response to contextual features of hospitals managing DR-TB, which included geographic setting, disease burden and patient social profile. Typically, clinical champions created 'workaround' solutions to resource constraints to meet policy objectives but required support from their organisational networks to ensure that their vision for policy implementation was sustainable. Important mechanisms of all clinical champions included resourcefulness, relationship building, collaboration and innovation. Disease-centred champions emphasised clinical governance and adopted a systematic approach to policy implementation to maintain quality of care. Patient-centred champions developed solutions to balance the clinical and social needs of patients.

**Conclusions:** In the South African context of decentralising DR-TB care, champions play a significant role in policy implementation and overcome barriers in resource-constrained environments and should, therefore, be nurtured, recognised and receive sufficient support.

## EP02 Challenges for randomised controlled trials on TB treatment

### EP02-110-21 International multicentre controlled trial to evaluate 1200mg and 1800mg rifampicin daily in the reduction of treatment duration for pulmonary tuberculosis from 6 to 4 months

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**Background:** The current treatment of drug-sensitive pulmonary tuberculosis (PTB) involves taking drugs daily for 6 months. A shorter treatment could result in greater cure rates. Pre-clinical and clinical (Phase II – HIRIF, RIFATOX) studies using higher doses of rifampicin have shown improved bactericidal activity to *Mycobacterium tuberculosis* and no increase in toxicity, respectively; which may have the potential to reduce treatment duration in humans. RIFASHORT is an international multicentre controlled clinical trial implemented with the objective to reduce the current 6 months regimen for PTB to 4 months using higher doses of rifampicin.

**Design/Methods:** The INTER-TB consortium at St George's University of London are conducting an open-label 3-arm controlled trial of 654 newly diagnosed, microscopy and GeneXpert positive, HIV negative and Rifampicin sensitive adult patients with PTB. The control regimen is ethambutol, pyrazinamide and isoniazid (EZH) plus 10 mg/kg rifampicin for the initial 2 months (intensive phase), followed by isoniazid and rifampicin (at the same dose size) for an additional 4 months (continuous phase) (2EZHR/4HR).

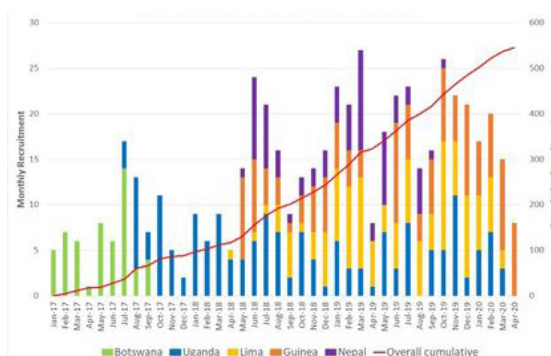
Study regimen 1 is 2 months of daily EZH and rifampicin at 1200mg followed by 2 months of daily isoniazid and rifampicin at 1200mg (2EZHR 1200/2HR1200).

Study regimen 2 is 2 months of daily EZH and rifampicin at 1800mg followed by 2 months of daily isoniazid and rifampicin at 1800mg (2EZHR 1800/2HR1800).

**Results:** The first participant was recruited in January 2017. At end of April 2020, we have completed 82% recruitment with 545 participants from 5 sites; Botswana 54, Nepal 70, Uganda 171, Guinea 131 and Peru 119. Of these, 87% have completed treatment and 45% have completed post-treatment follow-up.

Two additional sites have been included in Pakistan, and the recruitment at these sites is expected to commence in June 2020.

**Conclusions:** The trial ends in August 2021. We will have the complete analysis and results by early 2022.



[Figure. RIFASHORT recruitment January 2017 - April 2020]

### EP02-111-21 Documenting challenges faced and lessons learned from implementation of STREAM – the world's largest recruited MDR-TB clinical trial

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**Background:** Designing clinical trials for multidrug-resistant tuberculosis (MDR-TB) is complex[1] – multi-country clinical trials also face complexities of different regulatory requirements and variable infrastructure.[2] It is therefore important to document challenges and lessons learned – especially from trial sites' perspective – to ensure best practices are disseminated and implemented in future trials.

[1] Mitnick C, Rusen ID, Bain LJ, Horsburgh CR. Issues in design and interpretation of MDR-TB clinical trials: report of the first Global MDR-TB Clinical Trials Landscape Meeting. BMC Proceedings. 2015, 9 (Suppl 8):S1  
[2] Schluger N, Karunakara U, Leinhardt C, Nyirenda T, Chaisson R. Building Clinical Trials Capacity for Tuberculosis Drugs in High-Burden Countries. Plos Med. 2007; 4 (100):e302.

**Design/Methods:** STREAM recruited over 1,000 participants from 15 sites across the two stages of the trial. We conducted a voluntary survey, using Survey Monkey, of trial staff at all sites to obtain information on challenges encountered and lessons learned from trial implementation. Summary statistics were generated for quantitative data and thematic coding was done by two coders for qualitative data.

**Results:** Of 68 responses received, 19 were excluded (1 for no consent, 5 duplicate responses, and 13 incomplete responses) and 49 were included in the analyses.

Thirteen (87%) of fifteen sites from all eight STREAM countries responded, and approximately half were site investigators, physicians, or trial coordinators. Limitations in infrastructure was a challenge across key areas including laboratory, pharmacy, and trial administration. Complexities around import/export of drugs/samples and human resource challenges such as lack of prior experience, and inadequate training were also reported. Improved communication and coordination among all stakeholders, coupled with clarity around roles and responsibilities and robust oversight may improve successful implementation.

**Conclusions:** Upfront investment in infrastructure, enhanced coordination and communication, and ongoing capacity building are needed for successful implementation of clinical trials.

### EP02-112-21 A method for baseline adjudication of tuberculosis diagnosis in children in a therapeutic clinical trial: experience from SHINE

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**Background:** Diagnosis of TB in children is challenging and over-diagnosis is not infrequent. In 2015, an international expert panel revised consensus definitions for diagnostic studies for childhood pulmonary tuberculosis (PTB). SHINE is a phase III childhood TB treatment shortening trial, comparing 4 versus 6 months of standard therapy for drug-sensitive non-severe TB (ISRCTN63579542). The trial is powered assuming 20% children do not have TB. A key subgroup analysis is in children adjudicated by an independent clinical group to have TB at enrolment, according to consensus definitions. We describe a systematic method for defining this subgroup.

**Design/Methods:** A committee of paediatric TB experts (SG, JS, SW) was formed. Data items from the 2015 consensus case definitions were used, and in addition, as requested by the TB experts, weight-gain and growth parameters (height-for-age, weight-for-age) and peripheral lymph node description for TB adenitis cases (including site, size, and consistency). The adjudicating members were randomly assigned a set of approx.

800 SHINE participants for adjudication, blind to randomised arm. Cases were classified as “confirmed TB”, “unconfirmed TB” or “unlikely TB”. Discordant cases were sent to the third member.

**Results:** There was high concordance (81%) between the initial two members with 19% sent to a third reader. 163 (14%) cases were confirmed TB, 795 (66%) unconfirmed TB and 246 (20%) unlikely TB. 127 (16%) and 96 (39%) of the unconfirmed and unlikely TB cases were adjudicated by a third read respectively.

**Conclusions:** Diagnosing non-severe PTB in young children is challenging and results from SHINE will inform international guidelines for treating childhood TB. Results in children adjudicated as having TB disease will be essential. The approach used in SHINE can help to overcome challenges in the paediatric TB research studies in the absence of gold-standard diagnostic test of TB in children.

### EP02-113-21 Sustainability of the ACT4 randomized trial to improve initiation of TB preventive treatment

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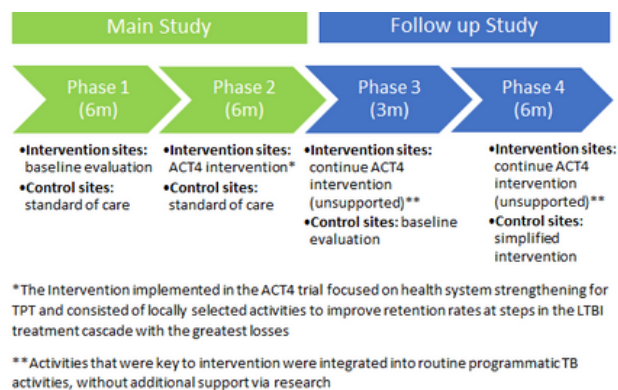
**Background:** Major efforts to strengthen health systems are required to increase TPT initiation rates and prevent TB globally. The ACT4 randomized trial, conducted in 24 health facilities in 5 countries, found that a health systems intervention to strengthen management for Latent TB Infection (LTBI) was effective at increasing TPT initiation rates in households contacts (HHC). In this follow up study, the sustainability of the ACT4 intervention was evaluated over the 9 months following the end of the trial.

**Design/Methods:** The main study and the follow-on study had 4 distinct study phases (Figure 1). To assess sustainability of the intervention, TPT initiation rates for HHC randomized to the intervention arm in the main study were compared between study phase 4 and phase 2.

The primary objective was to see if, without additional support or intervention, there was a significant change between study phases in the number of HHCs initiating TPT per 100 index cases. Sensitivity analysis was performed to consider if the effect was sustained over

different phases of the study. Marginal Poisson regression models that were corrected for clustering and few clusters and a log link were used to consider the differences between study phases.

**Results:** A small but non statistically significant decrease in number of HHC per 100 index cases was noted, with a difference of -9 (-26, 7) HHC initiating TPT per 100 index cases between phase 4 and phase 2. When data from both Phase 3 and 4 were combined and compared to Phase 2, a similar effect was found (-12 (-34, 9) HHC initiating TPT per 100 index cases).



[Figure 1. Study design]

**Conclusions:** In the nine months following the end of the ACT4 trial, the health system strengthening approach that was implemented continued to be effective at increasing TPT initiation rates in HHC once activities were integrated into routine programmatic TB activities.

### EP02-114-21 Utility of colour vision testing for screening for ethambutol-associated ocular toxicity in children treated for TB in the SHINE trial

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**Background:** Ethambutol-associated ocular toxicity (EAOT) is reported in 0.05-0.7% of children treated for drug-sensitive tuberculosis (DS-TB). Colour vision tests detecting red-green colour deficiency are used in adults for EAOT monitoring. Paediatric TB guidelines are inconsistent on the inclusion of ethambutol in treatment

for DS-TB and EAOT screening. We assessed the utility of a child-friendly colour vision test as a screening tool to identify clinically-significant EAOT.

**Design/Methods:** We evaluated Colour Vision Test Made Easy (CVTME) in children in the SHINE trial (ISRCTN63579542), conducted in Africa and India. CVTME is a validated screening tool for red-green colour deficiency in children aged  $\geq 3$  years.

**Results:** Of 1204 children recruited, 756 received TB treatment including ethambutol at WHO-recommended doses (15-25 mg/kg). A total of 661 children aged  $\geq 3$  years were eligible for CVTME (median [IQR] age 7[5, 10] years, 50% males); 468(71%) were on ethambutol; 62(9.4%) children, median age 4[3, 4] years, were unable to complete CVTME. Of 599 children who had CVTME, 4(0.7%) had abnormal CVTME at baseline and 2(0.5%) children, both on ethambutol, had new abnormal CVTME after baseline. Of the 4 children with abnormal CVTME at baseline, 3 had normal tests on repeat visits, and one child, subsequently diagnosed with CMV retinitis, had persistently abnormal tests.

Two children (HIV-negative, received ethambutol 22 and 18mg/kg for 8 weeks) had abnormal CVTME at 4 and 8 weeks, respectively with no visual complaints. The first child had normal CVTME at 8 weeks, the second had normal vision 3 weeks later on ophthalmology review.

**Conclusions:** There was no evidence of clinically-significant EAOT in children taking ethambutol in this large well-controlled trial. These results support previous data that ethambutol at WHO-recommended doses appears safe in children. CVTME testing in children is feasible, however it may not be necessary for those receiving standard treatment for DS-TB.

### EP02-115-21 Adolescents in a tuberculosis clinical treatment trial: characteristics of an underrepresented population

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**Background:** Tuberculosis (TB) in persons aged 10-19 represents nearly 10% of the global burden. However, this group is historically underrepresented in clinical

trials, potentially limiting their access to effective new treatment options. To better understand adolescent enrollment patterns in TB clinical trials, we examined data from a Tuberculosis Trials Consortium and AIDS Clinical Trials Group randomized, open-label, phase III, rifapentine-containing treatment shortening trial for pulmonary TB (S31/A5349; NCT02410772; Pharmaceuticals/PK testing; Sanofi).

**Design/Methods:** We conducted a descriptive analysis of individuals screened for and enrolled in NCT02410772, comparing adolescents (12-17 years) to adults ( $\geq 18$  years) in these preliminary results of demographic and clinical characteristics, reasons for non-enrollment, and HIV co-infection.

**Results:** Participants were enrolled at 34 sites in 13 countries; adolescents were enrolled at 10 sites in seven countries. Among 5,004 persons screened for study participation, 148 (3%) were adolescents. Compared to screened adults, more adolescents were female (54% vs. 33%) and born in Africa (86% vs. 74%). Enrollment of those screened was slightly lower in adolescents at 46% (68/148) than in adults at 50% (2448/4856). Non-enrollment reasons were similar in adults and adolescents: ineligible (81% vs. 79%), persons declined (13% vs. 15%), and site chose to not enroll (6% vs. 6%).

Of 68 enrolled adolescents, 59 (87%) were  $\geq 15$  years (range 13-17 years). Proportionally, compared to enrolled adults, more adolescents were born in Africa (85% vs. 73%), fewer were males (54% vs. 71%), and more had cavitation on chest x-ray (87% vs. 72%); no adolescents were HIV+ (0% vs. 9%) and fewer adolescents smoked (15% vs. 24%).

**Conclusions:** Adolescents were underrepresented in this trial. Since non-enrollment reasons and percentages were similar between adolescents and adults, efforts to augment adolescent participation should focus on recruiting and screening larger numbers of potential adolescent participants so this group could benefit from future novel treatments.

## EP02-116-21 Investigator-reported barriers and facilitators to adolescent recruitment, enrollment, and retention in TBTC study 31/ACTG A5349

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**Background:** The Tuberculosis Trials Consortium (TBTC) and the AIDS Clinical Trials Group (ACTG) evaluated barriers and facilitators to enrolling adolescents (12-17 years) into a randomized, open-label, phase 3, rifapentine-based treatment shortening trial for drug-susceptible pulmonary tuberculosis (S31/A5349; NCT02410772).

**Design/Methods:** We used the Capability, Opportunity, Motivation, and Behavior (COM-B) Model to develop in-depth interview guides. We conducted interviews using Zoom© with a convenience sample of 12 principal investigators (PIs).

Among the 12 interviews, we conducted six with TBTC PIs, three from adolescent-enrolling sites and three from non-adolescent-enrolling sites. Similarly, we conducted six interviews with ACTG PIs, three from adolescent-enrolling sites and three from non-adolescent-enrolling sites.

We recorded and transcribed all interviews, then annotated four transcripts to identify themes, developed a codebook with definitions and examples, and assessed inter-coder agreement. We used NVivo 12 Pro to systematically code and analyze all interviews.

**Results:** Investigators at adolescent-enrolling sites attributed their success to: recruiting from clinics that serve both adult and pediatric populations; selecting recruiters with ties to the community; placing recruitment staff onsite at recruitment locations; having previous experience working with adolescents; promoting awareness of TB through schools; being flexible to accommodate school schedules; recruiting from a site closer to schools; and demonstrating sensitivity to TB-related stigma.

Among the 6 investigators at non-enrolling sites, two reported they had obtained Institutional Review Board (IRB) approval and one reported the IRB disallowed



adolescent enrollment citing lack of safety data on rifampentine in adolescents. Three investigators reported no intention to enroll adolescents; of the three, two described governmental restrictions barring inclusion of adolescents in trials.

**Conclusions:** Specific site characteristics likely facilitate enrollment of adolescents into TB clinical trials. Regulatory obstacles may impede such enrollment. Knowledge of these features can assist efforts to increase adolescent participation in future TB clinical trials.

### EP02-117-21 Exploring antagonism in anti-tuberculosis drugs using a hollow-fiber model

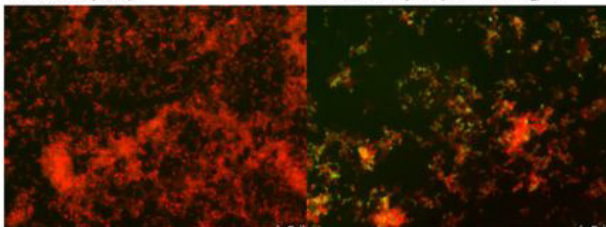
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**Background:** Isoniazid (H) and rifampicin (R) are critical in TB chemotherapy in the intensive and continuation phases. Rifampicin is a powerful sterilising agent in TB chemotherapy and higher dose regimens have shown promise. Using a hollow fiber model and an MTB surrogate species, *Mycobacterium komossense*, we have shown R/H together are less bactericidal than rifampicin monotherapy. Here, we explore how cell viability changes when *M. komossense* is exposed in the hollow fiber model.

**Design/Methods:** *M. komossense* was grown for 168 hours in the hollow fiber model and exposed to rifampicin and isoniazid alone and in combination. Bacterial viability was determined using with live/dead staining with Sytox green™ and resazurin as a marker for cell viability.

T0 - Isoniazid exposure; nil

T144 - Isoniazid exposure; 18 rounds of 1ug/ml



[Figure 1. *M. komossense* treated in the hollow fiber bioreactor with isoniazid at 1xMIC generates lipid bodies which have been shown to indicate a drug tolerant state.]

**Results:** At x1 MIC H numbers of “live” organisms rose after 48 hours from  $\sim 5 \times 10^5$  cells/mL to plateau at  $\sim 5 \times 10^8$  cells/mL. The number of “dead” bacteria rose from 0 cells/mL at T0 to  $\sim 1 \times 10^6$  cells/mL at T24 where it continued at this level until T168. Taking dual-stained as ‘injured’ they mirror the “live” bacterial pattern. For x9

MIC H the number of “live” cells increased steadily to plateau later at 96 hours. The x1 MIC H/R combination causes a rapid clearance from  $\sim 9 \times 10^5$  cells in 48 hours.

**Conclusions:** Isoniazid increases the more resistant lipid-rich cell population but this is not seen in combination with rifampicin. Our work emphasises the importance of exploring the interactions between regimen components.

### EP03 Digital technology in the fight against TB

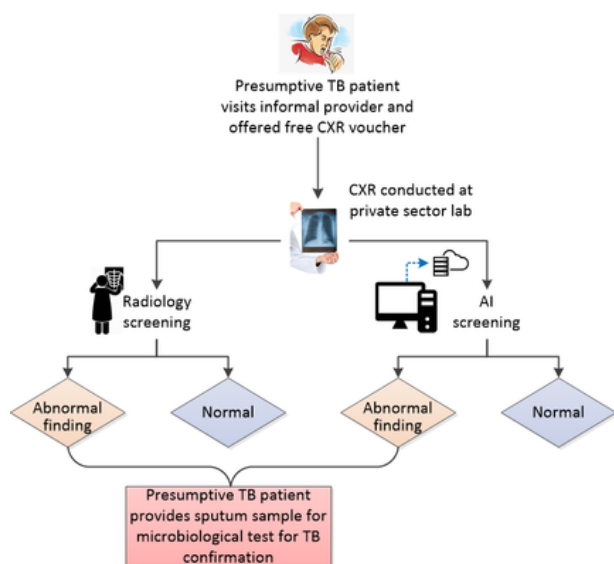
#### EP03-118-21 Implementation of artificial intelligence for presumptive TB screening in Nagpur, India

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**Background and challenges to implementation:** Countries, such as India, have increased efforts for tuberculosis (TB) case detection however limited capacity poses challenges. Chest x-rays (CXRs) are increasingly used at the programmatic level, however lack of human resources is a barrier. Thus, there is interest in emerging artificial intelligence (AI) technologies such as *qXR* developed by Qure.ai (Mumbai, Maharashtra). It identifies 15 CXR abnormalities of which eight are suggestive of typical or atypical pulmonary TB. PATH implemented a TB REACH intervention in a resource limited setting of Nagpur, Maharashtra where *qXR* was included as part of the screening algorithm.

**Intervention or response:** PATH mapped 33 CXR facilities of which six were included in the intervention. These facilities met the key requirements for *qXR* installation namely; a digital CXR machine with Windows 7 SP2, constant internet connectivity and DICOM software for image reading. The intervention engaged with 316 private informal providers who offered free CXRs to coughing patients for TB screening. CXRs were read by *qXR* as well as six radiologists and a positive reading (abnormal CXR) by either was reported as presumptive TB.

**Results/Impact:** From the six facilities, 8,303 patients were screened of which, 2,371 (28%) CXRs had abnormal findings either on AI and/or radiology. Upon comparing radiologist and *qXR* reports, 82% of CXRs had similar results. The project detected 29 (13%) additional TB cases confirmed microbiologically or clinically, which would have otherwise been missed without *qXR*.



[Figure. Sputum sample of presumptive TB patients with abnormal CXR findings were tested microbiologically for confirmation of TB.]

**Conclusions:** Our intervention demonstrates the added value of AI tools in resource constrained settings, where radiologists may be limited or unavailable, and emphasizes the need to scale up AI tools to accelerate the TB elimination efforts.

### EP03-119-21 Decentralised drug resistant tuberculosis treatment challenges in South Africa and options for implementation of a smartphone application based on latest guidelines

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**Background:** South Africa (SA) has the third highest number of notified cases of drug-resistant tuberculosis (DR-TB). We aim to develop and pilot a smartphone ap-

plication based on national guidelines, providing clinical decision-making support for healthcare workers (HCW) managing DR-TB

in adults and children in decentralised settings in SA. We present results from the first phase of this work in which online surveys and focus groups were used to explore existing barriers to guideline implementation.

**Design/Methods:** The Theoretical Domains Framework (TDF) was used to develop an online survey and interview schedule for in-depth focus group discussions. Two researchers analysed the data independently using the TDF as an analysis tool. Key domains were identified according to frequency of observations.

**Results:** 21 HCW responded to the online survey over a 3 month period (74% female; 57% medical officer; average 6 years' experience with DR-TB patient care; 43% urban decentralised primary care) and 14 HCW were involved in two focus groups (71% female, 71% physicians with DR-TB experience, 21% nurses, 57% urban decentralised primary care). 67% of survey respondents used the most up to date national guideline. 47% accessed PDF guidelines on their mobile phones. 37% found guidelines too long. Respondents felt least able to easily find information in relation to management of complications and least confident in applying them in paediatric populations. Junior practitioners often seek advice from senior colleagues via messaging apps. 95% felt a smartphone application as a decision support tool would be valuable. Two key 'user personas' - junior rural doctor and senior TB nurse - were identified to support the design of the app.

**Conclusions:** A smartphone application based on guidelines would be a popular tool in decentralised DR-TB care. The information from the survey and focus groups will be helpful to identify user groups and functionalities for creating the application.

### EP03-120-21 Disease patterns on computer-assisted chest radiography in a community-based prevalence survey for tuberculosis

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**Background:** Tuberculosis (TB) is one of the leading causes of death from a single infectious disease agent. Better screening and testing approaches are needed to improve TB screening and case finding. There is a grow-

ing interest in the automated analysis of chest x-rays as a sensitive and inexpensive means of screening populations for pulmonary TB.

**Design/Methods:** The SCALE study (Sustainable Community-wide Active Case Finding for Lung hEalth) is a cluster randomised trial investigating whether providing periodic TB/HIV active case finding leads to reduced prevalence of undetected adult infectious TB disease in Blantyre, Malawi. During the trial prevalence survey, participants were screened for TB using sputum for microscopy and Xpert MTB/RIF, as well as computer-assisted digital chest radiography (CAD-DCXR), and referred to a community-based clinic for evaluation if they had an abnormal x-ray based on radiographer assessment. We estimated prevalence of CXR abnormalities, described using the WHO Integrated Management for Adult Illnesses classification (IMAI), and how they related to CAD-DCXR interpretation.

**Results:** We screened 13,915 participants. 650 had abnormal CXRs and were referred to the clinic. 382 (58.8%) participants attended the community-based clinic. 92 (24.1%) were HIV positive, 92% of whom were on ART. 1 in 5 people were found to have hypertension, with 80% of them having an abnormal CXR. 21 (5.5%) were identified as active TB disease and were linked to health facilities for repeat microbiological testing and treatment initiation. The commonest causes of CXR abnormality was cardiomegaly ( $n = 83$  [21.7%]). The CAD-DCXR system described 61 (16%) to have abnormalities consistent with active TB, 34 (8.9%) having cardiomegaly and 47 (12.3%) having non-classifiable abnormalities.

Pathology	Overall (382)	Abnormal [209 (54.7%)]	Normal [173 (45.3%)]	p-value
Asthma	11 (2.9)	6 (54.5)	5 (45.5)	0.336
Cancer	5 (1.3)	4 (80.0)	1 (20.0)	0.336
Diabetes	8 (2.1)	6 (75.0)	2 (25.0)	0.336
Gastritis	15 (3.9)	8 (53.3)	7 (46.7)	0.336
Heart disease	93 (24.3)	90 (100)	0 (0.0)	<0.001
Chronic obstructive airways disease	33 (8.6)	33 (100)	0 (0.0)	<0.001
Old TB	40 (10.4)	40 (100)	0 (0.0)	<0.001
Hypertension	100 (26.2)	80 (80.0)	20 (20.0)	<0.001

[Table. Factors associated with any abnormal finding on chest X-ray]

**Conclusions:** This evaluation draws a broad picture of the burden of disease at community level in Blantyre, which consists of a large burden of undiagnosed non-communicable diseases, and the role of computer-assisted radiography in community-based disease screening.

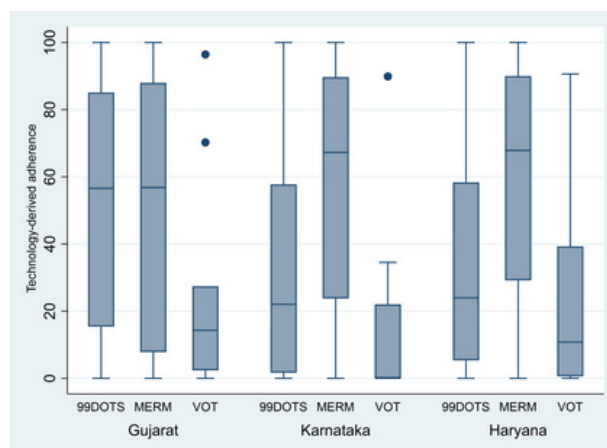
## EP03-121-21 Integrated digital adherence technologies for TB: determinants of technology-derived adherence

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**Background:** The Integrated Digital Adherence Technology initiative (IDAT) model deployed 99DOTS, Medication Event Reminder Monitor (MERM), and VideoDOTs (VOT) simultaneously across 8 districts in 3 states of Gujarat, Karnataka, and Haryana in India. Patients selected the technology most appropriate and accessible to them. Healthcare workers escalated patients based on missed doses—as indicated by IDAT signals—for further intervention.

**Design/Methods:** The quantitative sample consisted of 12,100 patients enrolled in IDAT over the period of May 15th 2019 to February 29th 2020. The primary outcome measure was technology-derived adherence, defined as the number of doses taken (as indicated by DAT signals) over the treatment duration period. Multivariate linear regression was used to evaluate systems, technology, demographic, clinical, and temporal factors associated with technology-derived adherence.



[Figure 1: Median/ IQR technology-derived adherence ( $n=12,100$ )]

**Results:** Median technology-derived adherence (t-adherence) across 12,100 IDAT patients was 47.0%. Median t-adherence was 46.3% for 99DOTS, 63.4% for MERM, and 10.1% for VOT. States with relatively weaker health systems had a lower t-adherence by -15.8 percentage points (95% CI -17.4, -14.3) and -18.9 points (95% CI -21.9, -16.0). Patients treated in the private sector had a lower t-adherence by -8.5 points (95% CI -10.3, -6.7) compared to the public sector. HIV positive and drug-resistant TB patients had a decreased t-adherence by -17.8 points (95% CI -20.9, -14.7) and -16.8 points (95% CI -24.8, -8.9) respectively, compared to new, drug-sensitive



cases. Age groups over 45 years had lower t-adherence. Patients in the continuous phase of treatment had a lower t-adherence by -6.8 points (95% CI -8.7, -4.9) compared to patients in intensive phase.

**Conclusions:** Variability in technology-derived adherence is observed across technologies and geographies. IDAT implementation is dependent on strength of health systems to absorb technologies and the capacity of healthcare workers to contextualize DATs within the broader patient experience of TB treatment and comorbidities.

### EP03-122-21 Implementing a referral system for drug-resistant tuberculosis patients to maximize treatment linkages to the public sector and minimize the treatment initiation time in Mumbai, India

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**Background and challenges to implementation:** In 2015, through the Private Provider Interface Agency (PIIA) intervention, 13,577 TB patients were diagnosed, out of which there were 1,245 drug-resistant TB (DR-TB) patients in 24 wards of Mumbai and around 20 percent of the patients initiated treatment in the public sector. Due to inadequate guidance and duration to the patients for pre-treatment evaluation (PTE) in public hospitals, there were considerable delays in linkages in the public sector and treatment initiation with the appropriate drug regimen. Therefore, PATH created a “test and refer model” where PATH provided PTE and drug susceptibility test (DST) free of cost to the patients in the private sector lab and patients were initiated on DR-TB treatment in the government hospital reducing the time for treatment initiation

#### Intervention or response:

- Treatment Coordinator (TC) followed up with the patients with RIF resistance through Cartridge Based Nucleic Acid Amplification Test (CBNAAT) results and informed the respective private doctor for further investigation.
- DR-TB patients underwent free PTE and DST tests. TCs referred these patients to the respective senior DOTs plus supervisor (SDPS). SDPS completed the relevant documentation of the patient to complete the linkage process.
- The patient along with the TC visited the DR-TB unit to initiate DR-TB treatment.
- TC conducted regular follow-up through home visits and calls for counseling and treatment adherence and ensure a positive treatment outcomes.

**Results/Impact:** In Mumbai where the linkages model was implemented, from March 2017 to August 2019, 1,398 DR-TB patients were diagnosed and 1173 (83%) were initiated on treatment in the public sector with an average duration of 15 days for linkage.

**Conclusions:** Effective referral mechanism with strong coordination and implementation strategy can result in successful DR-TB patient linkages from the private doctors to the public sector through established processes.

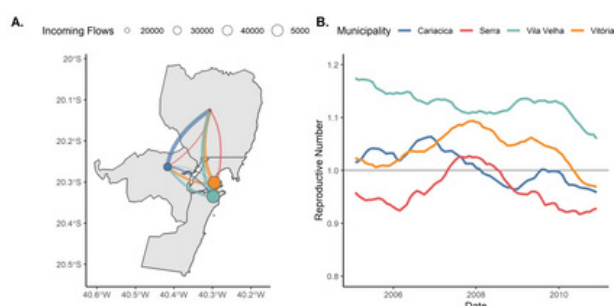
### EP03-123-21 Methods for estimating spatial and time-varying transmission patterns of tuberculosis in Espirito Santo, Brazil between 2005 and 2013

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**Background:** It is important to monitor changes in tuberculosis (TB) transmission dynamics and understand the impact of an area’s spatial and demographic characteristics. However, outside of research studies specifically designed and funded for this purpose, limited tools exist to understand these dynamics.

**Design/Methods:** We used data from the TB Notes surveillance system in Espirito Santo, Brazil, which has captured all microbiologically confirmed cases of TB since 2000. Using this data with an estimate of the serial interval, we assess time-varying reproductive numbers across the state’s four major municipalities. We incorporate mobility flows derived from a census-informed radiation model. To validate these estimates, we correlate them with a concurrent household contact and RFLP study conducted in the same region.

**Results:** Our results indicate variation in transmission patterns, with one municipality having sub-critical transmission values and three exceeding the critical threshold of one (Figure). We note that municipalities with lower reproductive number estimates tend to have less RFLP concordance between multiple cases in the same home, suggesting less autochthonous transmission. The municipality with the highest reproductive number estimate also reported the highest percentage of households with multiple members concurrently infected, while the second highest reproductive number is found in the state capital. These two regions collectively represent the majority of incoming mobility flows.



[Figure.]

**Conclusions:** It is possible to use routinely collected surveillance data to understand local transmission patterns of TB. This can be done in an ongoing manner and provide insight on transmission hot spots. Here we estimate that the state capital and adjacent city have higher incoming mobility flows and reproductive numbers. This dense region may serve as a reservoir of disease for the two more distant municipalities that, in isolation, would be unable to support continued disease transmission.

### EP03-124-21 eHealth in the future of TB medicines management: a case of a TB medicines web-based ordering and reporting system (TWOS) in Uganda

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**Background and challenges to implementation:** TB Medicine availability is the most effective intervention for improving health outcomes. In 2011 the TB supply chain was integrated into the national supply chain system. After the integration, there was a limited quantification capacity of TB medicines at lower level health facilities, less than 10% of stock cards correctly filled, delays in submitting the orders, and long lead time which resulted in low availability of TB drugs hence treatment interruptions.

In a bid to strengthen TB commodity management, the ministry explored the role of eHealth in TB medicines management,

**Intervention or response:** To improve TB medicine availability, the Ministry of Health adopted a TB medicines web-based ordering and reporting system (TWOS). Using the system, the health facility requisition is entered into an online tool for resupply from the central warehouse. The system implementation included training facility TB focal persons, medicine management supervisors and central warehouse staff in the proper use of the system. The system was piloted three districts, allowing for any system issues to be addressed before national roll-out. Monthly stock status dashboards were generated from the system to inform redistribution.

**Results/Impact:** The system provided real time monitoring of TB medicines stocks at treatment units, provided critical logistics and patient data thus improving the national quantification process. The timeliness of orders submitted to the central warehouse improved from less than 30% to 85%, the availability of TB medicines improved from 75.5% to 82% in 18 months. With visibility on the stock levels at over 1,290 health facilities, targeted redistribution was possible for over-stocked facilities hence the ability to minimize medicine wastage due to expiries.

**Conclusions:** The electronic ordering system facilitates information gathering for healthcare decision support, enhances the speed and accuracy of data transmission which improves National quantification for TB commodities. Additionally, it allows better stock monitoring thus ensuring uninterrupted medicine availability.

### EP03-125-21 How can we find TB patients not linked to care? Lessons learned from a systematic tracing process implemented in the Western Cape Province, South Africa

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**Background:** South Africa is a high-burden TB country with an estimated incidence of 520/100,000 population in 2018. All TB patients, irrespective of place of diagnosis, should attend a primary healthcare facility (PHC) for treatment. Patients not linked to a PHC after diagnosis are defined as initial loss to follow up (ILTFU). In 2016, the Western Cape Province diagnosed ~49 000 TB patients, and ~13 000 (26%) were not recorded in the TB treatment register. We describe lessons learned during a systematic process to find ITLTFU TB patients.

**Design/Methods:** We used the Western Cape Provincial Health Data centre with integrated routine health data sources into single patient records. We included all patients recorded as ILTFU after all the routine follow up health services in one sub-district in Cape Town between January and March 2020. Using an electronic data collection tool, study tracers systematically recorded process required to identify outcomes of these patients. We used a case descriptive analysis.

**Results:** Overall, 49 patients were defined as ILTFU and 21 (43%) were found. Of patients found, 19/21 (90%) were confirmed to be on TB treatment (Figure 1).



[Figure 1.]

Efforts required to contact patients varied, including: Checking health facilities' registers, speaking to community health workers about their previous search attempts, multiple telephone calls (dependant on contact

numbers) and asking local residents to assist in finding addresses. Of those not found; 18/28 (64%) was due to an invalid home address, largely within informal settlements.

**Conclusions:** Patients categorised as ILTFU in this setting were almost all on treatment. After correcting data capture and synthesis errors, additional effort to find patients truly ILTFU was extensive with limited yield. Focus should be on ensuring high quality data capture and collaboration with patients to ensure continuity of care.

### EP03-126-21 An assessment of the effectiveness of mobile community-based TB screening in Blantyre, Thyolo and Mwanza in Malawi

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**Background and challenges to implementation:** To demonstrate the effectiveness of TB screening through mobile vans equipped with TB geneXpert and digital chest X-ray (CXR) in diagnosing presumptive missing active TB cases.

**Intervention or response:** Since 2018, mobile vans equipped with TB diagnostic equipment were deployed in the communities to screen individuals suspected of having TB infection. Following community sensitization and mobilization, individuals who were willing and provided consent were screened in the mobile Van through chest X-ray and geneXpert. Pregnant women and those <15 years were tested only using geneXpert. Participants with abnormal findings on CXR and /or tested positive on geneXpert were referred to the nearest health center for treatment and further management.

**Results/Impact:** Within a period of 4 months, 4271 clients were screened for active TB infection with a slight dominance of females (52%). TB case notification rate was 3.1%. Only 24% of the cases were bacteriological confirmed. 52% of the cases were aged between 24-45 years old. 47% of the cases were known HIV infected and were on ART. 34% of the cases reported were previously treated of TB infection.

Site	clients screened (n)	presumptives (n)	TB cases (n%)
Health centers (OPD)	1833	359	79(22%)
Community	1448	191	34(18%)
Prison	807	132	17(13%)
Health care workers	183	46	3(7%)
TOTAL	4271	728	133

[Table 1: summary of all the cases and targeted population.]

**Conclusions:** TB screening through mobile Vans is a viable strategy in finding active TB missing case's in the communities. HIV/TB co-infection remains a prevalent morbidity in Malawi. Combined efforts for screening TB and HIV infections need to be enhanced in the Mobile vans screening program. Enhanced and mandatory screening through community outreaches and at health facilities is crucial in early detection of active TB, with subsequent timely referral for appropriate care and treatment.

### EP03-127-21 Decentralizing access to digital information management to treatment supporters level for efficient real-time patient management

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**Background and challenges to implementation:** Treatment Supporters (TS) are the last mile connectivity of the health care system with the patient. They counsel/ follow-up with patients daily till treatment completion and keep health staff informed about patient's health. They maintain records of daily adherence to medication, trigger followup visits and testing. They also receive incentives for successful treatment outcomes.

**Intervention or response:** If TSs can access and update patient's record directly in Nikshay, it would mean that the information digitized at the location and time of its generation. Further, registration of TS in Nikshay and mapping them to patients under care enables transparent and faster incentive payments via electronic transfer. The TSs can be registered in Nikshay and assigned to patients taking treatment in Public/Private Sector under the district. They can login and access treatment details of assigned patients and update necessary details and is accessible for further action throughout the levels of program hierarchy. The Banking details of the TS can also be recorded and incentives transparently processed to TS for all patients under his/her care, receiving successful outcome.

**Results/Impact:** By May 2020, over 174,000 TS are registered in Nikshay 1,31,990 patients have been assigned TSs in of which 99,420 have completed treatment. Over 83000 TSs incentives have been paid, amounting to over INR 85 Million. However, further decentralization of record keeping requires training and change management.

**Conclusions:** Enabling TS to access patient records in Nikshay and incorporating payment of TS incentives into the system has provided increased efficiency, effectiveness, transparency and accountability to the whole process.

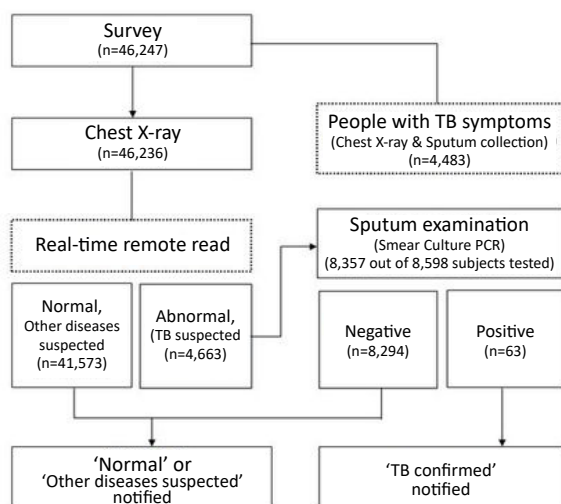
## EP04 Learning from epidemiological analyses

### EP04-128-21 Results of pulmonary tuberculosis (TB) screening for the elderly aged $\geq 65$ years in Korea, 2019

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**Background:** Among Korean patients with tuberculosis (TB), elderly population aged 65 or over showed TB incidence of 47%, mortality of 82%, and continues to increase. Thus, reduction in TB incidence and mortality of population cannot be achieved without reduction in TB incidence of elderly population. The Korea Centers for Disease Control and Prevention (KCDC) carried out TB screening project for early detection in 2019. The project aims to early detect-treat elderly TB patients and prevent TB transmission among elderly population.

**Design/Methods:** TB screenings were conducted for elderly in six-regions with high rate of TB. The methods included survey, chest X-ray (real-time-reading). Also, sputum tests (smear-culture-PCR) were conducted on the site for following people: coughing for 2-weeks or more, and history of TB or suspected of having active TB, based on results of interpretation of chest X-ray.



[Figure. Tuberculosis (TB) screening procedure  
\*Excluding 548 people who are TB symptoms and Abnormal]

**Results:** Survey, chest X-ray were conducted for 46,247 participants. The findings showed that 8,598 were suspected of having TB. 8,357 (18.1%) of suspected patients participated in sputum test, and 62 participants (134 per 100,000) were found to have been infected with TB. Patients had following characteristics: males (51.6%), aged 75 years or over (80.6%), underweightness (11.3%), medical-care-recipients (16.1%), smokers (33.9%), TB symptoms (21.0%), and TB history (22.6%). Patients with such characteristics showed high incidence of TB ( $p<0.05$ ). Although not statistically significant, most Patients were identified as elderly living in communities (83.9%). Chest X-ray results showed that 51.6% (32/62) of Patients had inactive TB. Sputum tests revealed that 30.7% (19/62) smear-positive, 88.7% (55/62) culture-positive, and 50.0% (31/62) PCR-positive.

**Conclusions:** Chest X-rays (real-time-reading), day-to-day sputum TB screening were carried out for elderly with high rate in TB incidence-mortality. This led to increase in TB screening rate and earlier detection of inactive TB patients on chest X-rays. We will continue to conduct TB screening for vulnerable elderly, and detect-treat TB patients at earlier stage. This way, we will help reduce the number of elderly TB patients.

### EP04-129-21 Excess mortality in TB patients diagnosed at hospital vs at primary health care in South Africa

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**Background:** In South Africa, low tuberculosis (TB) case detection and high overall case fatality remain important challenges. In the Western Cape Province, South Africa, patients diagnosed with TB at hospital level may start TB treatment but must typically attend a primary health care facility (PHC) for TB registration, and for treatment to be continued. We aimed to evaluate mortality in patients routinely diagnosed with TB at hospital and PHC in Cape Town, South Africa.

**Design/Methods:** Retrospective analysis of all routine TB data from the integrated provincial health data centre which harmonises all electronic health data sources. All patients with a laboratory or clinical diagnosis of TB at PHC, district or tertiary hospitals in 2 sub-districts of Cape Town, were identified between October 2018 and February 2020. Logistic regression was used to

investigate predictors of mortality and a Kaplan Meier survival curve described survival over time.

**Results:** Of 16,075 TB patients, 3,574 (22%) were diagnosed at hospital and 12,501 at PHC; 15,112 (94%) initiated TB treatment, and 14,057 (88%) linked to PHC for ongoing TB treatment. A total of 977 (6.1%) patients died, including 195 (20.3%) pre-treatment. Multivariable analysis suggested that age >25 years, HIV infection with and without ART, extrapulmonary TB, drug-resistant TB, failing to start TB treatment and hospital-based diagnosis were independently associated with higher mortality (Table). Of TB patients diagnosed at hospitals who did not start TB treatment, 70% died within 2 weeks of their diagnosis.

Predictors of mortality among all TB patients	Adjusted Odds Ratio (95%CI)
Age	
25-34 years vs 15-24 years	1.53 (1.11-2.1)
35-44 years vs 15-24 years	1.98 (1.44-2.73)
45-54 years vs 15-24 years	2.04 (1.47-2.85)
55-64 years vs 15-24 years	4.01 (2.84-5.66)
≥65 years vs 15-24 years	6.64 (4.58-9.64)
HIV Positive on ART vs HIV negative	2.21 (1.87-2.62)
HIV Positive no ART vs HIV negative	2.54 (1.92-3.36)
Extra pulmonary vs pulmonary TB	2.89 (2.31-3.61)
Drug resistant vs drug susceptible TB	2.46 (1.91-3.18)
Hospital diagnosed vs diagnosed in primary care	4.65 (3.99-5.42)
Not starting treatment vs starting TB treatment	3.94 (3.2-4.85)

[Table: Multivariable logistic regression model for significant predictors of mortality in all TB patients.]

**Conclusions:** Individuals diagnosed with TB in hospitals contribute significantly to TB-associated mortality. A TB diagnosis made at hospital level reflects more severe and advanced TB disease with possibly additional risk factors and higher mortality risk. TB patients diagnosed at hospital present an opportunity to identify those at high risk of early and overall mortality, where appropriate treatment should be rapidly initiated.

## EP04-130-21 A geopidemiologic approach to diagnose social inequities among vulnerable territories to tuberculosis in Northeast from Brazil

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**Background and challenges to implementation:** Tuberculosis has been present in humanity for millennia, being considered a serious disease, but curable. In the Americas region, it represents the second leading cause of death.

**Intervention or response:** To identify the social inequalities associated with the occurrence of tuberculosis in areas at risk of the disease. This is an ecological study, carried out in a city in the Northeast of Brazil. For the analyzes, the statistical model called Generalized Additive Models for Location, Scale and Shape was used, considered a semi-parametric regression model, given the need for a parametric distribution for the response variable. The selected distribution was Poisson Duplo, which is a special case of the double exponential family.

**Results/Impact:** Only the variable per capita income of ½ to 1 minimum wage remained in the final model, having a direct effect on the TB cases, that is, the increase in the number of households with this income in the urban census sectors of the municipality resulted in a higher average of cases of the disease. The variable proportion of men and women under the age of 15 in the census tracts, which showed a positive ratio and the proportion of men, but between the ages of 15 and 59, showed an inverse or negative relationship with the variance of cases in the census sectors. Thus, the variance or dispersion of the data decreases when there is a greater proportion of men between 15 and 59 years old and increases when a greater proportion of young people is found in the units of analysis of the study. It can be seen that income, education and housing conditions were factors related to the occurrence of tuberculosis, with great heterogeneity in its distribution.

**Conclusions:** TB control actions also need to include the elimination of social inequalities that can directly influence access to quality health care.



### EP04-131-21 Poor linkage to care and high mortality among pregnant women with tuberculosis in South Africa

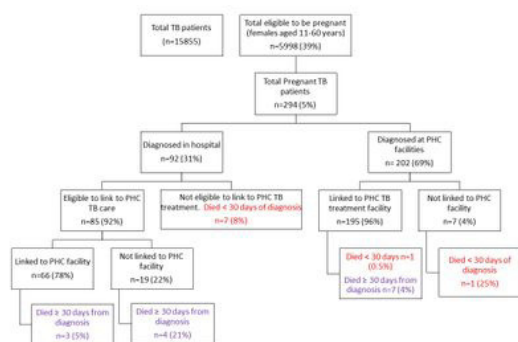
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**Background:** South Africa had an estimated 301,000 new cases of TB in 2018 and in 2014 there were an estimated 8,400 (2%) pregnant women with TB among 447,000 new cases. HIV co-infection among TB patients is 59% and ~30% of women receiving antenatal care are HIV-infected. Pregnant women with TB are at high risk of poor health outcomes, especially if not linked to care. We describe linkage to care among pregnant women routinely diagnosed with TB in Cape Town, South Africa.

**Design/Methods:** Utilizing the Western Cape Provincial Health Data Centre (PHDC), which integrates multiple sources of routine health data resulting in single patient records, we analyzed data for all pregnant women diagnosed with TB in 2 sub-districts in Cape Town (October 2018 to February 2020). Descriptive statistics were used to describe the cohort, stratified by location of diagnosis; hospital vs. primary health care (PHC) facility.

**Results:** Of 294 pregnant TB patients; 12/294 (4%) were < 20 years, 144/294 (49%) had previous TB treatment, 216/294 (73%) were HIV-infected, with the majority on ART at the time of TB diagnosis (186/216; 86%). One third (92/294; 31%) were diagnosed in hospital. TB-associated mortality was 8% overall (23/294) and 15% (14/92) among women diagnosed in hospitals. 9/23 (39%) TB deaths occurred within 30 days of diagnosis. Of those alive at 30 days after TB diagnosis, 19/85 (22%) diagnosed in hospitals and 6/200 (3%) diagnosed at PHC did not access TB treatment in a PHC facility (Figure 1).



[Figure 1.]

**Conclusions:** We document high mortality and high HIV co-infection among pregnant women diagnosed with TB in Cape Town. High rates of non-linkage to care among women diagnosed in hospitals highlights significant challenges in continuity of care. Pregnant women diagnosed with TB are a highly vulnerable group who require more intensive follow up to ensure linkage to care.

### EP04-132-21 Individual associated factors for developing tuberculous meningitis: a cross-sectional study

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**Background:** Diagnosis of tuberculous meningitis (TBM) is challenging. Associated factors among tuberculosis (TB) patient with developing TBM could help clinicians with TBM diagnosis, but little is known about it. We aim to evaluate which patients with TB are associated with increased risk of developing TBM.

**Design/Methods:** In this cross-sectional study, we included all TB inpatients from Jan 2008 to Dec 2019, in Beijing Chest Hospital (Beijing, China). Demographics (age, sex, ethnicity, origin, marital status, occupation), comorbidities (diabetes mellitus, kidney failure, connective tissue disease, pregnancy, HIV infection, malnutrition) and concurrent TB (table) were extracted from electronic medical records using a standardized data collection. Factors associated with TBM were identified by using univariate and multivariate logistic regression.

**Results:** 31264 patients were enrolled in this study, including 1167 (3.9%) patients diagnosed with TBM. The age of TBM patients (30.0, IQR 22.0-49.0) was younger than that of non-TBM patients (48.0, IQR 28.0-63.0). More than half patients were male in both TBM and non-TBM cases. Only 28 (0.1%) cases were HIV-positive in all.

In multivariate analysis, age < 60 years (1-14 years: adjusted odds ratio [aOR]: 3.466, 95% confidence interval [CI] 1.822-6.591; 15-29 years: aOR: 3.295 [2.411-4.502]); 30-44 years: aOR: 2.479 [1.867-3.290]); 45-59 years: aOR: 1.861 [1.391-2.370]), farmer (aOR: 1.669 [1.250-2.227]), not Beijing-born (aOR: 1.630 [1.338-1.987]), miliary pulmonary TB (aOR: 66.612 [56.428-78.635]) and splenic TB (aOR: 2.899 [1.240-6.775]) were independently associated with increased risk of developing TBM.

However, pleural TB (aOR: 0.556 [0.459-0.674]), cutaneous and soft tissue TB (aOR: 0.415 [0.277-0.623]), and osteoarticular TB (aOR: 0.490 [0.349-0.689]) were associated with lower risk.

**Conclusions:** Young, farmer, miliary pulmonary TB and splenic TB were associated with increased risk of developing TBM in TB patients. Screening TB Patients with these characteristics could facilitate clinicians to identify TBM patients at early stage.

Concurrent TB	Total (n=31264), n(%)	TBM (n=1167), n(%)	Non TBM (n=30097), n(%)	Bivariate, OR (95% CI)	P value
Miliary pulmonary TB	920(2.9)	553(47.4)	367(1.2)	72.96 (62.53-85.13)	0.000
Tuberculous pleuritis	6688(21.4)	182(15.6)	6506(21.6)	0.67 (0.571-0.787)	0.000
Lymph node TB	1709(5.5)	86(7.4)	1623(5.4)	1.396 (1.114-1.748)	0.004
Cutaneous and Soft tissue TB	1624(5.2)	34(2.9)	1590(5.3)	0.538 (0.381-0.76)	0.000
TB of the head and neck	147(0.5)	10(0.9)	137(0.5)	1.89 (0.992-3.601)	0.049
Splenic TB	65(0.2)	18(1.5)	47(0.2)	10.016 (5.799-17.299)	0.000
Urogenital TB	397(1.3)	43(3.7)	354(1.2)	3.214 (2.329-4.436)	0.000
Spinal TB	2758(8.8)	135(11.6)	2623(8.7)	1.370 (1.140-1.647)	0.001
Osteoarticular TB	1863(6.0)	52(4.5)	1811(6)	0.728 (0.549-0.966)	0.027

[Table.]

### EP04-133-21 Prevalence and risk factors of active tuberculosis in Chinese rheumatic patients: a multi-center, cross-sectional study

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**Background:** To investigate the prevalence and risk factors of active tuberculosis (ATB) in patients with rheumatological conditions in China.

**Design/Methods:** A tertiary hospital-based, multi-center, cross-sectional study was conducted between September 2014 and September 2015. 13 general hospitals were randomly selected from the eastern, middle and western part of China using a multi-stage cluster sampling strategy. Eligible patients with confirmed diagnosis of various rheumatic diseases were consecutively recruited and screened for ATB. The composition ratio of each rheumatic disease during the whole year of 2014 was collected to adjust the calculation of prevalence. Patients not taking anti-TNF biologics were included in the analysis of risk factors. Data about demographic features, underlying diseases and past and current medications were obtained.

**Results:** A total of 13550 patients with rheumatic conditions were enrolled. The adjusted prevalence of ATB according to the composition ratio of various rheumatic diseases was 882/100000 (95% confidence interval (CI): 706-1057). A total of 11649 patients were included in the risk factor analysis for ATB. Multivariate analysis showed that male (OR=1.929, 95% CI: 1.034-3.600), SLE patients (OR=2.772, 95% CI: 1.080-7.117), Behcet's disease (BD) patients (OR=4.375, 95% CI: 1.403-

13.640), having history of TB (OR=8.127, 95% CI: 4.395-15.031), taking Mycophenolate mofetil (MMF), Leflunomide (LEF), Cyclosporine A (CsA) over the past two years (OR=2.628, 95% CI: 1.093-6.318; OR=2.691, 95% CI: 1.243-5.824; OR=5.374, 95% CI: 1.464-19.719; resp) and exposed to glucocorticoids  $\geq 30\text{mg/d}$  more than eight weeks over the past two years (OR=2.111, 95% CI: 1.102-4.044) were independent risk factors of ATB.

	ATB	ATB included	Univariate analysis	P value	Multivariate analysis	P value
	n(%)	n(100%)	OR (95% CI)		OR (95% CI)	
<b>Gender</b>						
Female	43	9000	1		1	
Male	22	2465	0.539 (0.084-3.375)	0.276	0.509 (0.094-2.805)	0.009
<b>Age (years)</b>						
10-30	22	2303	1		1	
30-45	28	3406	0.774 (0.462-1.317)	0.373	0.762 (0.468-1.252)	0.389
45-60	25	4231	0.578 (0.325-1.017)	0.062	0.777 (0.389-1.532)	0.476
>60	9	1871	0.448 (0.211-0.912)	0.029	0.608 (0.328-1.102)	0.087
<b>Type of rheumatic diseases</b>						
RA	15	4026	1		1	
SLE	17	2780	0.758 (0.358-1.617)	<0.001	0.773 (0.386-1.517)	0.004
SS	8	1230	0.808 (0.377-1.746)	0.586	0.762 (0.341-1.714)	0.492
TM	4	654	0.449 (0.143-1.392)	0.196	0.759 (0.403-1.431)	0.446
UCTD	0	314	/		/	
PM	1	212	0.333 (0.075-1.517)	0.781	0.504 (0.129-1.898)	0.366
DM	1	306	0.508 (0.074-3.282)	0.571	0.382 (0.045-3.272)	0.380
MF	3	142	0.369 (0.109-1.281)	0.201	0.815 (0.258-2.572)	0.742
MS	1	276	0.788 (0.098-6.728)	<0.001	0.205 (0.048-0.908)	0.031
<b>Other systemic connective</b>						
AS	8	1075	0.506 (0.091-2.861)	0.406	0.768 (0.262-2.347)	0.618
PMR	0	111	/		/	
<b>Duration of Rheumatic Diseases (months)</b>						
0-30	43	9000	1		1	
30-120	11	1726	0.333 (0.096-1.170)	0.206	0.368 (0.122-1.051)	0.031
>120	12	1217	0.537 (0.248-1.171)	0.176	0.493 (0.210-1.091)	0.104
<b>Current use of immunosuppressants</b>						
CTX	6	1181	0.619 (0.209-1.812)	0.354	0.368 (0.129-1.095)	0.021
MMF	4	690	0.766 (0.287-2.132)	0.639	0.524 (0.191-1.412)	0.269
LEF	11	1711	0.742 (0.291-1.940)	0.501	0.422 (0.181-1.007)	0.054
ADA	6	238	0.788 (0.312-1.982)	0.619	0.519 (0.243-1.111)	0.091
UPT	2	2100	0.369 (0.084-1.617)	0.020	0.303 (0.088-1.041)	0.032
CSA	0	309	/		/	
TNF $\alpha$	1	144	0.830 (0.128-5.675)	0.893	/	
SASP	1	864	1.126 (0.142-8.942)	0.876	0.768 (0.142-4.202)	0.744
None	6	981	0.538 (0.247-1.171)	0.127	0.628 (0.375-1.047)	0.061
<b>Use of immunosuppressants over the past two years</b>						
CTX	16	1071	0.819 (0.370-1.770)	0.616	0.468 (0.202-1.071)	0.087
MMF	11	716	0.237 (0.103-0.574)	0.012	0.228 (0.109-0.506)	0.001
ADA	16	2819	0.708 (0.411-1.206)	0.217	0.279 (0.169-0.506)	0.003
UPT	6	287	0.811 (0.238-2.808)	0.614	0.461 (0.201-1.041)	0.012
LEF	11	1179	0.525 (0.245-1.100)	0.100	0.401 (0.203-0.839)	0.011
CSA	0	309	0.296 (0.127-0.692)	0.004	0.205 (0.104-0.408)	0.001
PMR	1	121	0.378 (0.149-1.000)	0.048	/	
SASP	6	711	0.608 (0.404-0.916)	0.008	0.377 (0.242-0.596)	0.014
None	6	986	0.797 (0.386-1.616)	0.503	0.433 (0.242-0.780)	0.017
<b>Current dosage of GC (mg/d)</b>						
0	22	4101	1		1	
0-15	19	4196	0.476 (0.058-3.916)	0.038	0.362 (0.181-0.711)	0.007
>15	28	1138	0.675 (0.387-1.165)	0.071	0.539 (0.328-0.882)	0.011
<b>Duration of GC (mg/d) over the past two years (months)</b>						
0-6	54	9006	1		1	
6-8	7	460	2.431 (1.167-5.076)	0.020	0.488 (0.217-1.111)	0.019
8-12	21	1191	0.870 (0.708-1.061)	<0.001	0.711 (0.512-0.989)	0.034
>12	11	981	0.510 (0.409-1.100)	<0.001	0.325 (0.198-0.539)	<0.001
<b>History of active TB</b>						
Yes	11	981	0.510 (0.409-1.100)	<0.001	0.325 (0.198-0.539)	<0.001

[Table. Potential risk factors of ATB in patients with rheumatic diseases]

**Conclusions:** The prevalence of ATB was significantly higher in rheumatic patients compared to the general population. Male, patients with SLE or BD, having a history of TB, previous exposure to immunosuppressants including MMF, LEF, CsA and moderate to high dose of glucocorticoids were independent risk factors for ATB in rheumatic patients without using anti-TNF biologics.

### EP04-134-21 Geospatial determinants of TB active case finding among men and working-age adults in Lima, Peru

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**Background:** Men and working-age adults are often difficult for TB case-finding programs to reach despite bearing disproportionately high TB burdens in many settings. We aimed to identify screening locations with good attendance among males and working-age adults in Lima, Peru.

**Design/Methods:** We analyzed data from a screening program in which an x-ray van visited 216 sites in northern Lima over 1 year. We calculated the percentages of attendees who were male and who were of working age (15-44 years), by site. We used a Wilcoxon rank-sum test to compare these percentages between sites at health facilities, transport terminals, markets, and general community locations. We used the Getis-Ord statistic to investigate spatial clustering among sites with higher percentages of males or working-age adults. We assessed whether sex or age was associated with whether people were screened within 1 km of their neighborhood of residence.

**Results:** The percentage male attendees was higher at transport terminals (median 65%, IQR 62–69%) than at community locations (median 39%, IQR: 36–42%,  $p < 0.01$ ), and lower at health facilities (median 34%, IQR 31–39%,  $p < 0.01$  compared to community locations). The percentage working-age adults was also higher at transport terminals (median 46%, IQR 44–51%) than at community locations (median 41%, IQR 36–44%,  $p < 0.01$ ). Sites with higher percentages of males were spatially clustered, even after excluding transport terminals ( $p = 0.02$ ). However, sites with higher percentages of working-age adults were not significantly clustered ( $p = 0.11$ ). Compared to women  $\geq 45$  years old, men  $\geq 45$  years old were similarly likely to be screened near their residences (73% for both,  $p = 0.89$ ), as were working-age women (74%,  $p = 0.12$ ). However, working-age men were less likely to be screened near their residences (70%,  $p = 0.01$ ).

**Conclusions:** Active case-finding in areas around transport terminals may offer opportunities to increase TB diagnoses among men and working-age adults.

### EP04-135-21 Geo-spatial mapping of tuberculosis burden in Anambra state South-East Nigeria

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**Background:** Anambra state in south-east Nigeria is one of the high TB burden states in the country. Despite recent improvements in TB case finding and notification, estimates from the National Prevalence survey suggest that there is still a significant pool of missed TB cases in the state. Although active TB case finding interventions are needed at the community level, information on local TB hotspots is crucial but sparse. The objective of this study was to map the geo-spatial location of all drug-susceptible TB cases detected in 2019 in the state. Findings from this secondary data analysis will help to target interventions appropriately with a view to achieving better program efficiency.

**Design/Methods:** A de-identified dataset containing the physical addresses of all registered TB cases in 2019 was developed. The dataset was deconstructed and restructured using Structured Query Language (SQL) in a relational database environment. The validated dataset was geocoded using ArcGIS server geocode service and validated using python geocoding toolbox, and Google Geocoding API.

The resultant geocoded vector data was subjected to geospatial analysis and the magnitude-per-unit area of the TB cases was calculated using the Kernel Density function. Choropleth maps were plotted to portray the TB burden as contained in the dataset.



[Figure.]

**Results:** Anambra Geospatial TB-Map Onitsha North, Onitsha South, Idemili North, Nnewi North, and Ogbaru Local Government Areas (LGAs) had spots with 'Extremely high' burden with Onitsha North and South accounting for the largest spots. Extremely high TB



burden was found mostly within the urbanized towns. Eight LGAs had spots with 'Very high' TB burden. 24 hotspots across the state had 'High' TB burden and two LGAs (Orumba North, Orumba South) had only 'Low' TB burden areas.

**Conclusions:** Visualizing the density map of TB burden in the state helps to identify transmission hotspots that can be targeted for active TB case finding interventions.

#### **EP04-136-21 Factors associated with health seeking behavior of persons to be evaluated for tuberculosis aged 15 years and above in Indonesia: tuberculosis prevalence survey**

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**Background:** Indonesia has the third-highest TB burden after India and China. Furthermore, there is still a huge gap in TB case detection rate. This paper aims to examine the health seeking behavior of people to be evaluated for TB in Indonesia.

**Design/Methods:** This study included 7523 people to be evaluated for TB aged 15 years old and above based on the Indonesia TB Prevalence Survey 2013-2014. We classified health seeking behavior into three categories: seeking healthcare facility, self or traditional treatment, and not seeking treatment. We examined risk factors within the initial behavior model (predisposing characteristics, enabling, and need factors). This study used analysis of variance to examine the association of factors in the initial behavior model and used multinomial regression models to improve the interpretability of the estimate and risk factors of people seeking self or traditional treatment and not seeking treatment.

**Results:** In this study, 75.4% (5672) of persons to be evaluated for TB had inappropriate health seeking behavior (seeking self or traditional treatment and not seeking treatment). We found that people to be evaluated for TB who were younger age (15-30 years old), males, people with low education levels, people with inadequate TB knowledge, smokers, and people who lived in a rural area were more likely to not seek treatment. People with middle-level education and urban residence were more likely to seek self or traditional treatment.

**Conclusions:** There is a big number of people to be evaluated for TB who have inappropriate health seeking behavior. These findings show there are missed opportunities for diagnosing and reporting TB among people who have TB symptoms. Increasing the attention of TB health seeking behavior among younger people, males, people with low education levels, and inadequate TB knowledge, smokers and people in rural areas is necessary to effectively achieve TB detection and control in Indonesia.

#### **EP04-137-21 Seasonality and trend of tuberculosis incidence rate after GeneXpert MTB/RIF era: a study in a vulnerable region from Brazilian Eastern Amazon**

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**Background:** Although Brazil adopted the GeneXpert MTB/RIF test for diagnosing tuberculosis mainly in metropolitan areas in 2014; there are few studies that have been conducted to evidence the impact of this test mainly in vulnerable areas. Some studies concluded that the technology alone was not sufficient to impact early diagnosis, since health systems continue to operate in the same mode without computerizing records and integrating the laboratory with health services. This study aimed to analyze the incidence of TB cases, its seasonality as well the trend of disease after the implementation GeneXpert MTB/RIF test.

**Design/Methods:** Ecological study in Macapá, capital of the state of Amapá, region of the Brazilian Eastern Amazon. We applied the Interrupted Time Series method for diagnosing seasonalality and the Prais-Winsten method to classify the event trend.

**Results:** The temporal trend of tuberculosis in Macapá from 2001 to 2017 was classified as stationary (0.002; 95% CI = -0.021; 0.026), however, through the sine and cosine variables related to the period of the year, it was possible to identify that tuberculosis in the municipality presents seasonality with growth of 13.7% / year (95% CI: 4.71; 23.87) in the periods between December and June referring to the rainy season called Amazonian winter and a decrease of 9.21% / year (95% CI: -1.37; -16.63), period referring to the hottest seasons. We observed an increase of 2.09% per year (95% CI: 0.92; 3.27) in the incidence of tuberculosis after the implementation GeneXpert MTB/RIF test.

**Conclusions:** We observed that GeneXpert MTB/RIF test has increased the TB detection rate; besides that the disease evidenced seasonality, with growth in the winter and decrease in the warmest period. The results contribute to understanding the dynamic and pattern of the disease and therefore to subsidize the health services and surveillance.

### EP04-138-21 Tuberculosis incidence rates and their determinants: an ecological multi-country analysis, 2005-2015

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**Background:** Accelerating the decline in tuberculosis (TB) incidence is paramount for achieving goals set by the Sustainable Development Goals and End TB Strategy. This study evaluated associations between recent trends in intermediary determinants of health and national TB incidence.

**Design/Methods:** The analysis took a longitudinal, country-level ecological design between 2005 and 2015. A total of 115 countries remained after excluding for missing data. The outcome was TB incidence per 100,000 population estimated by the World Health Organization. Associations between TB incidence rates and 16 indicators of material circumstances, behaviours, biological and psychosocial factors, health systems and TB programmes were estimated overall and stratified by country income group in univariable and multivariable Poisson regression models with country-level fixed effects and robust standard errors.

**Results:** The sample included 35 high-income (HIC), 34 upper-middle-income, 30 lower-middle-income (L-MIC) and 16 low-income (LIC) countries. Over follow-up, mean change in TB incidence rate was -25.97 per 100,000 (SD: 48.21). In multivariable analysis, changes in HIV prevalence and daily smoking were positively associated with change in national TB incidence rates ( $p=0.027$ ;  $p=0.033$ , respectively).

Change in access to clean fuels and technologies for cooking was negatively associated with change in national TB incidence rates ( $p=0.036$ ). Material circumstances, behaviours, biological factors and TB programme performance were most strongly associated with TB incidence in LICs and L-MICs. Psychosocial factors were most strongly associated with TB incidence in HICs.

**Conclusions:** Access to clean fuels and technologies for cooking, smoking, and HIV prevalence were dominant intermediary determinants of changes in global TB incidence. Further action on key social determinants of health may accelerate declines in TB incidence and help achieve global goals. Distinct approaches may be required across country income groups.

### EP04-139-21 Risk factors for mortality among patients with multi-drug resistant TB in Uganda: a case-control study

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**Background:** The WHO end TB strategy aims to reduce TB associated mortality to less than 5% by 2035. However, mortality due to multi-drug resistant tuberculosis (MDR-TB) is particularly high and stood at 15% globally for the 2016 cohort. In Uganda, MDR TB associated mortality was 19% in the same cohort. We set out to delineate risk factors for mortality among a cohort of patients diagnosed with MDR-TB in Uganda.

**Design/Methods:** We conducted a case-control study nested within the national MDR-TB cohort. We defined cases as patient who died from any cause during the two years following treatment initiation. We selected two controls for each case from patients alive and on MDR-TB treatment at the time that the death occurred (incidence-density sampling) and matched the cases and controls on health facility at which they were receiving care. We performed conditional fixed effects logistic regression to identify the risk factors for mortality. Missing data on alcohol use, previous TB treatment and education was handled using multiple imputation chained equations (MICE) with 30 imputations.

Characteristics	Un adjusted OR (95% CI)	P-Value	Adjusted OR (95% CI)	P value
<b>Age</b>				
0-17	0.16 [0.02-1.51]	0.11	0.17 [0.01-1.92]	0.15
18-34	0.51 [0.21-1.30]	0.16	0.61 [0.21-1.81]	0.38
35-49	0.40 [0.16-1.02]	0.06	0.42 [0.15-1.24]	0.12
50+	[1]		[1]	
<b>Education</b>				
None	3.40 [1.3-9.2]	0.02	3.61 [1.1-11.6]	0.03
Primary	1.90 [0.78-4.6]	0.16	2.02 [0.8-5.30]	0.15
Secondary & above	[1]		[1]	
<b>HIV status</b>				
Negative	[1]		[1]	
Positive	1.84 [0.98-3.50]	0.06	1.9 [0.93-3.90]	0.08
<b>Missed DR-TB doses</b>				
No	[1]		[1]	
Yes	1.73 [0.9-3.10]	0.11	2.20 [1.02-4.51]	0.04
<b>High risk group</b>				
No	[1]		[1]	
Yes	0.40 [0.12-1.60]	0.22	0.60 [0.11-2.24]	0.40

[Table 1. Conditional (fixed effects) logistic regression model of risk factors associated with mortality among patients with MDR TB]

**Results:** Data from 198 patients (66 cases and 132 controls) started on DR-TB treatment from January 1st to December 31st 2016 was analyzed for this study. Majority of patients (60.4%), were male and HIV positive (55.3%). About half (46.9%) were aged 18-34 years. On multivariate analysis, no education (aOR 3.61 95% CI [1.1-11.6]  $p=0.03$ ) and non-adherence to MDR-TB

treatment (aOR of 2.2 95% CI [1.02-4.51]  $p=0.04$ ) were associated with increased mortality. HIV Co-infection was also associated with an increase in mortality although it did not reach significance (aOR 1.9, 95% CI [0.93-3.90]  $p=0.08$ ).

**Conclusions:** Lack of education and non-adherence to TB treatment were major risk factors for mortality among patients diagnosed with MDR-TB. Patients with these risk factors should be identified and prioritized for additional support by the National TB program.

## EP05 Person-centred care: the advantages and challenges

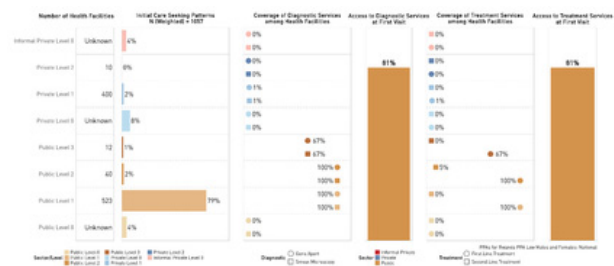
### EP05-140-21 Using Patient Pathway Analysis in Rwanda, methods, problems and the importance of data and sensitivity analysis

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**Background:** Tuberculosis ranks third in causes of death in Rwanda. Late diagnosis and treatment may contribute to mortality. There is limited information on access to care for persons with TB symptoms in Rwanda. Therefore, the aim was to assess alignment of health care seeking behavior and TB service availability using the Patient Pathway Analysis (PPA) including validation of PPA input parameters. Results will inform national strategy planning and programming and delivery of patient-centered care.

**Design/Methods:** The PPA was completed using 2014/15 DHS data and Master facility list at national level, the primary measures being place of initial care seeking, TB diagnostic locations and TB treatment locations. To validate input parameters we conducted sensitivity analyses using different definitions for the primary measures.

**Results:** According to the PPA, 2974 persons experienced symptoms of TB and 1047 (35%) sought care for these symptoms. The majority (79%) sought care at the public health center. All public health centers had diagnostic capacity (GeneXpert (3%), sputum smear microscopy (29%)) or sample transportation (71%) and can provide first-line treatment. Diagnostic service coverage was highest among district/ provincial hospitals. Second-line treatment was available at two district/ provincial hospitals (5%). Access to diagnosis and treatment at first visit was 81%. Sensitivity analysis showed that access to diagnostic and treatment is lower (52%) if the care seeking data of children with fever is used as a proxy for TB care seeking.



[Figure.]

**Conclusions:** Care seeking and service availability are well aligned in Rwanda. Divergent results can be obtained from the use of different parameters and definitions and seeking care for fever in children was not reflective for care seeking for TB in Rwanda. Sensitivity analyses should be conducted as part of PPA to estimate the effects of using different datasets and variables for initial care seeking, TB diagnostic locations and TB treatment locations.

### EP05-141-21 Improving surveillance data quality in Nikshay introduction of machine assisted de-duplication

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**Background and challenges to implementation:** To close the gap of missed TB notification, Government of India has made it mandatory for all healthcare providers including clinics, hospitals, laboratories and pharmacists to notify TB cases via the national surveillance and TB patient management system Nikshay. This brings along a potential risk of duplicate notifications based on where all the same patient seeks care throughout the duration of treatment for laboratory testing and medications.

**Intervention or response:** To reduce the probability of possible duplicates from entering the surveillance system, a two point machine assisted de-duplication mechanism was implemented in Nikshay. The combination of gender and phone number are used to identify potential duplicates. First, whenever users provide details matching existing records, an alert is provided to the user with the details of the original record. Users may stop entry and continue against the original record. If user decides skip the warning and continue, then the notification is flagged as a “potential duplicate”, requiring a manual verification and as a unique notification by an administrative user.

**Results/Impact:** Between June 2019 and April 2020,

over 2 million TB Patients have been notified, of which approximately 0.1 million cases have been identified by Nikshay as potential duplicates. It has prevented an unknown number of duplicates at the time of entry itself. Of the potential duplicates, about 30% have been manually verified as actually unique and 10% as actually duplicate; resulting in a positive predictive value of approximately 25%.

**Conclusions:** The method of utilizing the phone number and gender appears to be having an acceptable solution providing a positive predictive value of 25% for identifying duplicate notification (after the first user skips the warning). Other variables and algorithms need to be explored to improve the negative predictive value, sensitivity and specificity of this method.

### EP05-142-21 The paradox of free TB care in private for-profit private care facilities

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**Background and challenges to implementation:** DOTS introduction in 1994 institutionalised TB Control in Ghana and as a free health service disease. The free treatment covers diagnosis to treatment completion. Health services delivered in private for-profit facilities requires cost reimbursement either out of pocket or through health insurance. This has made public health interventions unattractive to private for-profit health facilities globally and in Ghana.

**Intervention or response:** The Aurum institute implement a pro-poor TB case finding health intervention in private for-profit facilities in Ghana using Public Private Mix (PPM) approach. A health system perspective cost effectiveness study was conducted where only costs incurred by the programme were considered. Four cost components were considered: Programmatic cost, Personnel cost, Capital cost and Technical assistant cost, summed up to form Total Programme Cost (TPC).

**Results/Impact:** The cost profile across intervention sub-metros was similar largely due to personnel cost accounting for over 90% of TPC. The total cost of programme for the intervention group was USD 997,602.65 excluding Aurum costs and that of the control was estimated at USD 287,620.51, an almost 4 folds higher costs in intervention site. The estimated TPC for the intervention sub-metros, exclusive of Aurum costs, ranged from USD 36858.45 to USD 127,111.01 and for the control sub-metros USD 7,773.50 to USD 77,735.18.

**Conclusions:** The provision of a public health intervention within private for-profit facilities is morally appealing but faced with the challenge of economic overhead costs. In the implementation of PPM-DOTs models, business operational costs must be considered and incentive packages tailored specifically to mitigate costs of provision of TB care service. In addition, stating all

the above, it is a simplistic view to take if the posture is taken that private sector engagement is too expensive without consideration of its antecedent factors.

### EP05-143-21 Pillar 2 of End TB strategy: impact of bold policies and supportive systems on program implementation in India

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**Background and challenges to implementation:** Government of India launched a scheme for nutritional support - "Nikshay Poshan Yojana" (NPY) for all TB patients registered in the online portal "Nikshay" of National TB program. This scheme entails transfer of 500 INR every month throughout the course of treatment directly into the bank account of the beneficiary. In addition, the government has identified 117 high priority (aspirational districts) which are monitored from highest level in the government.

**Intervention or response:** In this article, we document the difference in implementation of NPY in 117 aspirational districts against the remaining 644 districts under the programme. The article presents an analysis of secondary data collected through Nikshay portal under the National TB programme extracted at end of June and July 2018. Beneficiaries considered include those diagnosed with TB and registered from 01st April 2018 to 30th June 2018 and have completed at least 1 month of treatment.

**Results/Impact:** As on 31st July 2018, nearly 60,579 eligible beneficiaries were identified across aspirational districts, among whom more than 65% (39,248) bank account details were seeded and 23% (13,822) had received the payments.

In the remaining districts, almost 427,634 eligible beneficiaries were identified, among whom only 52% (222,010) bank account details were seeded and 13% (57,310) had received the payments. The rate of improvement in July 2018 as compared to June 2018, was nearly 2-3 times in aspirational districts as compared to remaining districts.

	Aspirational District Eligible Beneficiaries	Aspirational District Bank account seeding status	Aspirational District Payments done status	Remaining districts Eligible Beneficiaries	Remaining districts Bank account seeding status	Remaining districts Payments done status
	33681	49%	7%	230491	46%	9%
July 2018	60579	65%	23%	427634	52%	13%
Improvement		33%	229%		13%	117%

[Table.]

**Conclusions:** Intensive monitoring had an impact on the achievement in NPY in aspirational districts. Political commitment with adequate resources supports imple-

mentation of newer initiatives under the programme and the UN High level meeting should advocate for greater commitments from all governments for a TB free world.

### EP05-144-21 Comparison and analysis of different MOA (Mode of Administration) for TB treatment in PNG

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**Background:** Papua New Guinea (PNG) is one of the 30 high TB burden countries in the world. Around 85% of the population lives in rural areas with poor access to health care. This study compares treatment outcomes in TB patients using 3 modes of administration (MOA) including directly observed treatment (DOT) by treatment supporters, self-administrated treatment (SAT), and Family model (FM) in the Gulf Province. We also assessed adherence in a small cohort of Multidrug resistant (MDR) TB patients on SAT or FM.

**Design/Methods:** We performed a retrospective analysis of data from Quarter 3 2019 for drug-sensitive (DS) TB and all year 2019 for MDR TB. In total, we analysed 81 DSTB patients and 9 MDR TB patients. MOA was assessed with a checklist. All patients were offered 3 PEC sessions (initiation, 2 weeks and end of intensive phase), family members counselling, weekly visits by treatment supporters and transportation fees. MDR TB patients were also offered monthly PEC sessions and food support. A system of missed appointment tracing was in place.

**Results:** Treatment success is 85% for patients on SAT and 86% on the FM, compared to 72% for DOT. The LTFU rate is high at 21% for DOT model, compared to FM and SAT models at 7% and 10% respectively. All MDR TB patients, 1 on SAT and 8 on FM, achieved more than 80% adherence, and 6 reached 100%.

**Conclusions:** The study findings highlight the difficulty to correctly implement DOT, especially for patients living in limited or no access to health services areas, while suggesting that patients can be empowered to adhere to treatment with alternative models when an adequate support system is in place.

### EP05-145-21 Patient-centered tuberculosis treatment support tools: a mixed-method randomized controlled pilot study exploring initial efficacy and refinement needs

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**Background:** The SARS-CoV-2 (COVID-19) pandemic and resulting lockdowns are projected to have a devastating impact on global tuberculosis (TB) burden in the coming years. Alternative options, such as digital health technologies, could help TB programs continue services. Objectives were to assess the initial efficacy and refinement needs of the TB treatment support tools (TB-TSTs) intervention that links a mobile app, an in-home direct adherence drug metabolite test, and interactive communication with a treatment supporter.

**Design/Methods:** A mixed-methods pilot study was conducted within a public respiratory-specialized reference hospital in the Province of Buenos Aires, Argentina. Patients newly diagnosed with TB who were 18 or older and had mobile phone access were randomized to usual care ( $n = 21$ ) or the intervention ( $n = 21$ ). Primary outcomes were feasibility and acceptability; secondary outcomes explored initial efficacy. Multiple data collection methods were used to summarize intervention use, issues, and refinement needs.

**Results:** For those randomized to the intervention, interactions between participants and treatment supporter focused on promoting adherence through missed report inquiries and check-ins. Although there was a decrease in interactions over time, adherence support remained needed throughout. App related support was largely due to login issues. Over half reported side effects and requested assistance. Higher rates of treatment success were seen in the intervention group. Although not all intervention participants reported daily, none abandoned treatment. Only participants in the intervention group had follow-up sputum tests to be classified as cured.

**Conclusions:** Interactive communication was considered an essential intervention component. The efforts of the treatment supporter resulted in timely and effective handling of participant needs and created a sense of partnership. Potential solutions were identified for issues and findings are being used to iteratively refine the intervention. The refined TB-TSTs will be evaluated in a randomized controlled trial with ~400 participants at four public hospitals in Argentina.

### EP05-146-21 Evaluation of the accuracy of 99DOTS digital adherence technology for tuberculosis in Metro Manila, the Philippines

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**Background:** Patients with poor treatment adherence to tuberculosis (TB) treatment regimens have higher rates of unfavorable outcomes. Unfortunately, the Philippines has no standardized approach to monitoring treatment compliance in the private sector, where approximately half of the Filipino patients receive treatment. Implementing 99DOTS, a digital adherence tool (DAT) featuring a low-cost mobile phone-based technology that enables real-time remote monitoring of daily drug intake, could help support the country's United Nations high-level milestone by 2022. In this context, this study evaluated the accuracy of this novel DAT.

**Design/Methods:** Utilizing a cross-sectional cohort of consenting patients enrolled in the 99DOTS program, IsoScreen assay urinalysis tests were done in three pilot NTP-engaged private clinics in Metro Manila. The test was conducted randomly at the clinic at the time of their return visit for a medication refill. Positive (per urine testing) was identified by blue or purple findings while negative (per urine testing) was based on no change in the urine color. After comparing to their 99DOTS adherence status, positive predictive value (PPV), negative predictive value (NPV), and sensitivity were analyzed.

**Results:** A total of 103 eligible patients participated, of which 78 (75.7%) were males. The mean treatment time on the day of urine testing was  $3.24 \pm 1.59$  months. The majority (94.17%) was adherent based on the DAT platform dashboard. IsoScreen testing revealed that 101 (98.1%) were adherent based on urinalysis. Descriptive analyses showed the following: PPV=97.9%, NPV=0.0%, and sensitivity=94.1%.

**Conclusions:** Our study shows that 99DOTS adherence status is corroborated by the IsoScreen used to represent true adherence status. However, of the few non-adherent (according to 99DOTS dashboard) participants, the IsoScreen also showed recent medication ingestion. Conducting a multi-site cohort study, purposively sampling non-adherents, should be done to better measure the utility of 99DOTS to represent adherence before scaling up for nationwide adoption.

### EP05-147-21 Fully oral RR-TB treatment regimens: progress in removing injectable agents from high TB burden country policies

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**Background and challenges to implementation:** In 2018, the World Health Organization (WHO) issued consolidated guidelines that strongly recommended fully oral regimens as the preferred option for MDR-TB treatment. A Rapid Communication recommending a shorter, all-oral, bedaquiline-containing regimen was released in December 2019. Information on country level progress is lacking.

**Intervention or response:** The #StepUpforTB 2020 study aims to assess policy-adoption of international best practices and innovations on TB diagnosis, prevention and treatment in 43 high TB burden countries by the end of December 2019. A semi-structured questionnaire was used to interview National TB Programme managers or assigned focal points. A desk review of national policy documents was carried out as part of the data review. The overall response rate was 84%.

**Results/Impact:** As of December 2019, the standardized, injectable-based shorter regimen may still be used routinely according to national policies in 26/36 countries. 21/26 countries recommend amikacin as the preferred injectable agent, while five countries also indicate capreomycin and kanamycin may be used. 33/36 countries recommend a longer all-oral regimen for treating complex RR-TB for adults, either for routine use (started or completed in 28 countries) or in operational research conditions (started, completed or planned in 4 countries). Shorter all-oral regimens are indicated in 20/35 countries, with the majority of them (15/20) prioritizing operational research over programmatic implementation.

**Conclusions:** While operational research has supported increasing access to shorter all-oral RR-TB regimens, full countrywide transition to all-oral RR-TB regimens is slow, and a number of countries are still recommending injectable agents despite a negative recommendation for their use by the WHO. Urgent attention and support is needed to ensure rapid phase out of injectable agents for routine RR-TB treatment.

### EP05-148-21 Patient-centred care for drug-resistant TB: responding to diverse clinical and social circumstances

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**Background:** Patient-centred care, care that considers the needs and circumstances of individual patients, is one of the three pillars of the WHO End TB strategy. While South Africa has a policy of decentralised care for drug-resistant TB (DR-TB), that aims to deliver treatment closer to patients' residences, healthcare remains poorly responsive to the socio-economic and psychological needs of patients. We aimed to describe the complex medical, social, economic and geographic profiles of DR-TB patients.

**Design/Methods:** 195 patients (15 per district) diagnosed with rifampicin-resistant TB in the third quarter of 2016 were randomly selected from 13 districts across three provinces in South Africa (Eastern Cape, Western Cape and KwaZulu-Natal). Districts were purposely selected to reflect varied levels of decentralisation and urban-rural characteristics. One patient was excluded due to misdiagnosis. Laboratory and patient folder records were reviewed, patient home addresses were geolocated and the distance the patients travelled to healthcare facilities was calculated.

**Results:** Among the 194 patients, 62% were male, median age was 35 (IQR =28-44), 12% had XDR-TB, 63% were recorded to have had previous TB, and 69% were HIV positive. 36/65 (55 %) of patients with available data had viral loads >1000 copies/ml and 20/92 (22%) had CD4 < 50 cells/ $\mu$ l. Comorbidities ranged from infections related to immunocompromise to chronic conditions, including mental health conditions (n=12) and

mobility impairment (n=4). Only 43 patients were reported to be employed. Other socio-economic challenges included childcare commitments (n=24) substance abuse (n=17), and ill family members (n=17). 16% of patients travelled > 20km and 42% of patients travelled > 20 km to reach their diagnosing and initiating healthcare facility, respectively.

**Conclusions:** Patients experienced complex medical and social challenges, which belie a one-size-fits-all model of care. Service delivery needs to be differentiated in order to better address specific needs and vulnerabilities of individual patients.

### EP05-149-21 Perspectives on access to tuberculosis health services in Shigatse, Tibet, China

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**Background:** There is pressing need to ensure access to quality TB care for remote and rural populations in Tibet, China where the 2014 TB prevalence rate was almost twice the national average. Given the vast travel distances, difficult terrain and harsh weather, ensuring access to ongoing care poses numerous operational challenges.

However, little is known about the perspectives of people with TB accessing care in the region. Thus, our study aims to explore these experiences and perspectives on access to TB care in Shigatse, Tibet, China.

**Design/Methods:** We conceptualize access to healthcare drawing on a framework by Levesque et al., which explores five abilities comprising accessibility. We conducted 10 semi-structured interviews in Shigatse, Tibet. Interviews lasted between 30 minutes and 1 hour and were conducted with Tibetan interpretation. Participants were purposively sampled from a list of participants in an eHealth intervention trial. Informed consent was obtained, and interviews were audio-recorded and transcribed. Transcripts were checked by a native Tibetan speaker for accuracy. Two research staff conducted framework analysis using deductive and inductive approaches. Data was analysed using NVivo 12 software.

**Results:** Nine persons with TB and one family member were interviewed. Ability to perceive the need for TB care was informed by health literacy and beliefs, as well as expectations of healthcare providers. There were differing abilities to seek care, informed by personal and social views of the need for TB care. There were several transport and mobility challenges reported impacting ability to reach care. There were few challenges in abil-

ity to pay for treatment, however some reported costs of travel, food, traditional medicines, and lost wages. Patients reported their ability to engage and most described commitment to completing treatment.

**Conclusions:** There is need to strengthen access to TB care in Shigatse by reducing transport challenges and secondary costs of treatment.

### EP05-150-21 Beyond free medical care: Why TB patients seeking treatment in NTP facilities still face catastrophic expenses in the Philippines?

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**Background:** To determine the drivers of costs faced by TB patients and to estimate the proportion of TB-affected families facing catastrophic cost.

**Design/Methods:** A cross-sectional survey of 1,880 TB patients seeking treatment in NTP facilities—780 drug-sensitive (DS) patients in rural facilities, 780 DS patients in urban facilities, and 320 drug-resistant (DR) patients— from more than 188 facilities. Catastrophic expense is measured as costs related to TB care exceeding 20 percent of annual family income.

**Results:** The average total cost of TB treatment is \$463. For DSTB patients in rural facilities, it is around \$427. The total cost of treatment is slightly higher for urban DSTB patients at \$482 but considerably higher for DRTB patients at \$2,127. Income loss accounts for more than 50 percent of the total cost of TB.

Thirty-five percent of TB-affected families face catastrophic expense due to TB. The proportion is largest among DR patients at 88 percent, followed by rural DS patients at 38 percent, and urban DS patients at 24 percent respectively. Transportation and food during consultation and income loss account for the bulk of the cost faced by patients with catastrophic expense.

**Conclusions:** TB-affected families especially DRTB cases still face high costs due to travel and food expense and income loss. Results indicate the need for cost-mitigation strategies particularly in helping families manage the loss of income due to TB as well as the provision of a more meaningful social and health insurance coverage for TB care in the country.

### EP05-151-21 Short- and long-term outcomes of video observed tuberculosis treatment among patients in Chisinau, the Republic of Moldova

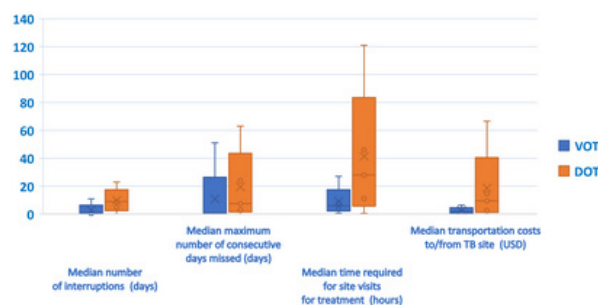
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**Background:** The Republic of Moldova is one of the most densely populated countries of the former Soviet Union and tuberculosis is a priority issue of public health. To support patient-centered interventions, a key element of the End Tuberculosis (TB) Strategy, Asynchronous Video Observed Treatment (VOT) in addition to Directly Observed Treatment (DOT) was piloted. A study was carried out to compare the results of using VOT and DOT among susceptible TB patients within three months of their outpatient treatment from 2016 to 2017 in Chisinau – the capital city.

**Design/Methods:** A randomized controlled trial involved 169 susceptible TB patients (≥18 years), were retrospectively reviewed: 83 on VOT and 86 on in-person DOT. Treatment strategies were compared using Chi-square test and Relative Risk at 95% confidence intervals.

**Results:** The mean age of participants was at about 38 years in both groups, with more than half (57% in VOT and 55% in DOT) being men. As referring to the short-term outcome, 99% of patients on VOT completed treatment compared to 94% on DOT (p=0.11). The proportion of observed treatment doses with VOT compared to DOT was higher (98.5% vs. 56.1%; p<0.001). A relative risk of 2.6 (p<0.001) for not taking medicines for at least consecutively 5 days was estimated in DOT-group. 30% of patients on VOT self-reported side effects compared to 21% on DOT (p=0.12). The study found that VOT reduced the travel time by 4.4-fold (p<0.01) and the transportation costs to TB sites (2\$ vs. 10\$) for TB patients (figure 1). Participants on VOT reported very high levels of satisfaction (100%; p<0.001) and strongly recommended (95%; p<0.001) it to other TB patients. For the long-term outcome, 4.7% of TB patients who received DOT developed relapses.





[Figure. Comparison of TB treatment adherence, travel time and transportation costs for VOT vs DOT treatment strategies during 3 months, Chisinau, Republic of Moldova, 2016-2017]

**Conclusions:** VOT reduced required time and travel costs for treatment while maintaining high levels of adherence and favorable treatment results.

## EP06 TB: data matters

### EP06-152-21 Assessment of tuberculosis underreporting by level of reporting system in Lagos, Nigeria

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**Background:** Nigeria is a high TB, TB/HIV and MDR-TB burden country with an estimated TB prevalence of 219/100, 000 population. Nigeria has only 24% TB treatment coverage and contributes 9% of the missing TB cases globally. The estimated TB underreporting was 42% in Lagos State.

The objective of the study was to Assess TB underreporting by type and level of health facilities including associated factors.

**Design/Methods:** The study design was a quantitative descriptive study using secondary data from an inventory study on TB reporting knowledge, attitude, and behavior conducted in 2017 in Lagos State, Nigeria. Chi-square and binomial logistic regression were used to assess the association between TB underreporting and the

characteristics of health facilities (HFs), health workers' (HWs) awareness, barriers to TB reporting, and patient-related factors.

**Results:** At least 60% of all HFs underreported TB with an average of 7.4% underreporting between HFs records and TB program reports. There was a statistically significant association between NTP nonengaged health facilities ( $\chi^2(1) = 20.547, p < 0.05$ ), HWs' awareness of TB reporting ( $\chi^2(1) = 6.576, p < 0.05$ ), and barriers for TB reporting ( $\chi^2(1) = 4.106, p < 0.05$ ) with TB underreporting.

The following patient factors were statistically significant predictors of TB underreporting with over 50% increased odds,  $p < 0.05$ : previously treated, extrapulmonary, unknown TB site, HIV negative, and HIV unknown.

**Conclusions:** TB underreporting occurrence was among all health care facilities (public, private, and the NTP engaged) and TB program should ensure a coordinating mechanism for TB reporting within and between HFs.

### EP06-153-21 Improving TB treatment outcomes through effective linkage of transfer out patients

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**Background and challenges to implementation:** Poor treatment success rates has been a great challenge for Homabay County especially the referral hospital which hosts most of the TB patients in the County.

This was due to the fact that there were no proper structures of following up the transfer out patients who constitute more than 70% of the total clients diagnosed with TB at Homabay County referral hospital.

In 2015 the facility registered a treatment success rate of 86% and 80% in 2016. This was below the 90% target for the quality of care indicator.

**Intervention or response:** Due to lack of specific TB tool for transfer-out, the facility designed and introduced a transfer out tool that is used to summarize patient information for proper linkage to the receiving facility. This has made transfers-out much easier and effective since most critical information needed for patient management are captured in this tool. It has also improved documentation in the TB treatment register.

**Results/Impact:** The introduction of the transfer out tool improved TB treatment success rates from 86% in 2015 to 97% in 2018. The tool also made it easier to account for all the TB patients being transferred out of the facility to their preferred sites.

The table shows the trend in treatment success rates from 2015 to 2018 for Homabay County hospital.

Year	Cured	Died	LTFU	TC	MT4	Grand Total	Treatment complete+cured	Treatment success rate
2015	52	9	3	43	0	111	95	86%
2016	42	15	2	57	0	123	99	80%
2017	84	24	0	171	0	279	255	91%
2018	125	13	1	361	1	501	486	97%

[Table.]

**Conclusions:** In conclusion, the introduction of the transfer out letter improved the treatment success rates from 86% in 2015 when it had not been introduced to 97% in 2018. Accounting for the transfer out patients also became easier as from 2017 April transfer out data could be retrieved compared to 2015 and 2016 where there was no data. Thus, the results revealed that the existence of a referral letter to a facility of choice is helpful in terms of follow up during treatment thus improved TB outcomes.

### EP06-154-21 Nationwide surveillance of emerging isoniazid resistance after implementation of Isoniazid Preventive Therapy for tuberculosis contacts

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**Background:** The monitoring of isoniazid resistance at both population and individual levels is crucial for implementation of Isoniazid preventive therapy (IPT) program.

**Design/Methods:** The results of drug susceptibility test (DST) testing on isolates were presented for both IPT and control groups and the estimated isoniazid resistance at population levels was calculated in reverse by confirming levels of isoniazid resistance proportional to bacteriological confirmation. For contacts who developed TB after IPT, M. tuberculosis isolates of paired index patients and contacts were compared with spoliotyping and 10-loci MIRU-VNTR typing.

**Results:** From April 2008 to December 2018, a total of 85301 latent tuberculosis infected (LTBI) contacts whose index patients identified as no isoniazid resistance were enrolled in our study and were followed until June 2019. Given an equal distribution of isoniazid resistance for those who received neither culture nor the

DST test in either group, the estimated rate of isoniazid resistance was 0.33 vs 0.48/1000 ( $p=0.471$ ) at population levels for the IPT group and the control group (Table). For the 193 LTBI contacts who developed TB during the study period, 49% developed TB before receiving IPT, 12% developed TB due to premature cessation of IPT, 4% developed TB during IPT, and 35% developed TB after completion of IPT. Isoniazid resistance was not statistically significant for those developed TB before receiving IPT compared to other groups (6/95 vs. 12/98,  $p=0.157$ ). 88% (117/133) of paired M. tuberculosis isolates were genotyped successfully and was matched in 61% of pairs. Eight out of 71 contacts (11.2%) developed new isoniazid resistance.

		IGRA(+) or TST(+)	Incidence Rate	MTBC	DST	INH Resistance	the Estimated Persons of INH Resistance		
							N	n(%)	n(%)*
Total	no LTBI treatment	34008	576(1.7)	257(44.6)	237(92.2)	15(6.3)	16	0.48	0.471
	Enter LTBI treatment	51293	193(0.4)	126(65.3)	125(99.2)	17(13.6)	17	0.33	
Controlling for age									
0-12	no LTBI treatment	6575	55(0.8)	23(41.8)	18(78.3)	1(5.6)	1	0.19	1.000
	Enter LTBI treatment	15687	38(0.2)	25(65.8)	25(100)	3(12.0)	3	0.19	0.482
13-17	no LTBI treatment	2009	49(2.4)	19(38.8)	19(100)	1(5.3)	1	0.50	1.000
	Enter LTBI treatment	4580	30(0.7)	13(43.8)	13(100)	4(30.8)	4	0.87	
18-29	no LTBI treatment	6908	134(1.9)	39(29.1)	36(92.3)	2(5.6)	2	0.31	1.000
	Enter LTBI treatment	7506	32(0.4)	22(68.8)	22(100)	3(13.6)	3	0.40	
30-64	no LTBI treatment	14567	205(1.4)	96(46.8)	90(93.8)	8(8.9)	9	0.59	0.071
	Enter LTBI treatment	18333	58(0.3)	38(65.5)	37(97.4)	3(8.1)	3	0.17	
65-79	no LTBI treatment	2468	69(2.8)	43(62.3)	42(97.7)	2(4.8)	2	0.83	1.000
	Enter LTBI treatment	3681	22(0.6)	16(72.7)	16(100)	2(12.5)	2	0.54	
>80	no LTBI treatment	1481	64(4.3)	37(57.8)	32(86.5)	1(3.1)	1	0.78	1.000
	Enter LTBI treatment	1506	13(0.9)	12(92.3)	12(100)	2(16.7)	2	1.33	

\*:MTBC/TB  
 \*\*:DST/MTBC  
 \*\*\*:INH R/DST  
 LTBI: latent TB infection; IGRA: interferon gamma release assay; TST: tuberculin skin test; MTBC: M. tuberculosis; DST: drug susceptibility test; INH: isoniazid  
 Footnote  
 \* The Estimated Persons of INH resistance = number of persons with positive culture for MTBCx proportion of DST results available for those with culture positive for MTBC x proportion of INH resistance among those with DST results  
 \*\* P-value for Fisher Exact Test and Cochran-Mantel-Haenszel statistic for stratification analysis  
 # "per 1000" means the estimated persons of INH resistance \*1000 / persons with LTBI (IGRA positive or TST positive)

[Table.]

**Conclusions:** No significant difference in isoniazid resistance was detected at population levels after long-term observation. Because there is an increased risk for isoniazid-resistant TB after exposure to IPT at the individual level, isoniazid DST is recommended for individuals who have developed TB after IPT.

## EP06-155-21 Review of the Epidemiological Mathematical Modelling Literature to Inform Tuberculosis Vaccination Development and Strategies

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**Background:** Mathematical models play an important role in the development, evaluation, and implementation of tuberculosis (TB) vaccines. A 2016 systematic review by Harris et al. provided an overview of the modelling literature and potential population-level impact of TB vaccines. The review highlighted the need for an improved evaluation of the setting-specific impact of different vaccines, age targeting of vaccines, and assessment of multidrug-resistance in future models. We updated the review and assessed whether the identified gaps have been addressed.

**Design/Methods:** PubMed, Embase, and the WHO Global Health Libraries were searched on 5th April 2020. Modelling studies were included if they assessed novel TB vaccination and reported population-level outcomes. Additional unpublished research was included based on expert input. Data collation included vaccine characteristics and epidemiological impact.

**Results:** Nine new studies were included. Findings suggested that, if prioritising impact by 2050, vaccine development should focus on preventing disease in *Mtb*-infected populations, but vaccines preventing infection or disease in uninfected populations may be useful in higher transmission settings. Studies suggested that the impact of age targeting depended on the underlying epidemic. For China, an aging, reactivation-driven epidemic, a post-infection vaccine targeted to older adults may have the greatest impact. Pre-infection vaccines had a larger impact in populations with transmission-driven epidemics. Spatially targeting hotspots or risk groups tended to increase the efficiency of vaccine strategies, and vaccines tended to be cost-effective when accounting for multidrug-resistant TB.

**Conclusions:** Tuberculosis vaccine modelling research has provided useful new information over the past four years, by exploring the differential impact of vaccine characteristics, age targeting of older adults, spatial or risk group targeting, and dynamically accounting for multidrug-resistant TB. Future models could provide evidence on the full value proposition of TB vaccines, more realistic implementation strategies, and estimating the value of information to reduce uncertainties about BCG revaccination and M72/AS01<sub>E</sub> impact.

## EP06-156-21 Strengthening hospital DOTS linkage using ad hoc staff to find missing TB cases: the Aminu Kano Teaching Hospital experience

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**Background and challenges to implementation:** In 2018 Nigeria simultaneously accounted for 4% of global Tuberculosis (TB) cases and 12% of the global TB notification gap, yet 60% of TB financing remains unfunded.

Aminu Kano Teaching Hospital (AKTH) is the largest tertiary facility in Kano state with an average daily hospital attendance of 862 patients. AKTH has 16 clinical departments and a staff strength of 1,150 persons across all cadres.

**Intervention or response:** The onion model of the patient care cascade depicts different steps in care seeking to the point of treatment outcome and predicts fraction drop offs at all levels starting from health facility attendees.

Eighteen Ad hoc staff were engaged, trained and deployed to service delivery points (SDPs) for active screening of all hospital attendees' daily, generating TB presumptive and ensuring prompt investigation through chaperone service up to treatment initiation. This intervention lasted for five months from 30-04-2019 to 30-09-2019.

**Results/Impact:** A total hospital attendance of 130,035 clients was recorded during this period of which 63,804 persons (49.1%) were screened leading to 3,773 presumptive TB (5.9%) identified and 152 cases (0.2%) diagnosed. Cumulative comparison to same period of previous year depicted a 411% increase in presumptive identification and 58% increase in TB patients notified.

**Conclusions:** Systematic use of trained ad hoc staff to screen all attendees at SDPs increases overall TB case notification at facility level. Passive case finding at high volume facilities potentially contributes to missed cases among a population subset with good health seeking behavior.

The study demonstrates the urgent need for a rethink of the current role of the facility TB DOTS unit from a TB patient registration, treatment and anti-TB drug pharmacy to a more agile unit organically expanding to coordinate facility wide active TB screening and chaperone service.

### EP06-157-21 Incorporating patient reporting patterns to evaluate geographically targeted tuberculosis interventions in Dhaka, Bangladesh

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**Background:** Tuberculosis is geographically heterogeneous, and geographic targeting can improve the impact and efficiency of TB interventions. However, standard TB notification data may not sufficiently capture this heterogeneity. Better understanding of patient-reporting behavior (discrepancies between patients' place of presentation and place of residence) may improve our ability to use notifications to appropriately target interventions.

**Design/Methods:** Using local demography data and TB reports from Dhaka North (DNCC) and Dhaka South (DSCC) city corporations, we identified wards of high TB incidence (i.e. "hotspots") and developed a mathematical model of TB transmission. We calibrated the model to patient-level data from selected wards in DNCC and DSCC under four different assumptions regarding patient-reporting behavior, ranging from perfect correlation to least-assumed correlation between patients' ward of presentation and ward of residence. Under each assumption, we estimated the relative impact of targeted active case finding (ACF) and preventive therapy (PT) for TB, compared against an untargeted intervention of equal intensity.

**Results:** The impact of geographically targeted interventions varied substantially depending on assumptions regarding patient-reporting behavior. The relative reduction in TB incidence, comparing targeted to untargeted ACF in DNCC, was 1.08 assuming least-assumed correlation between reporting and residence, versus 1.88 assuming perfect correlation. Similar patterns were seen in DSCC (1.19 versus 2.25) and when evaluating PT (1.16 versus 1.83 in DNCC, 1.28 versus 2.14 in DSCC).

Intervention Strategies	Reporting Behavior Assumptions			
	Perfect Correlation	Zero Correlation	High-Bound Estimate	Low-Bound Estimate
<b>Dhaka North</b>				
Active Case Finding (ACF)	87.8%	84.0%	81.9%	8.0%
Preventive Therapy (PT)	82.7%	89.7%	94.4%	16.1%
Combined ACF/PT	51.6%	60.9%	66.1%	-1.2%
<b>Dhaka South</b>				
Active Case Finding (ACF)	124.6%	66.8%	19.5%	19.3%
Preventive Therapy (PT)	114.0%	58.2%	18.7%	28.0%
Combined ACF/PT	87.8%	84.0%	81.9%	8.0%

[Table.]

Relative reduction in TB incidence, comparing targeted to untargeted interventions in Dhaka, Bangladesh. "High bound" assumes 50% of patients report TB in

their ward of residence, 37% in adjacent wards, and 13% in farther wards ("Low bound": 18%, 12% and 70%, respectively).

**Conclusions:** Better understanding of patient-reporting patterns can improve estimates of the impact of targeted interventions in reducing TB incidence. Movement of individuals seeking diagnoses may substantially affect TB transmission at the ward-level. Incorporating high-quality patient-level data is critical to optimizing TB interventions.

### EP06-158-21 Lessons from a Data Quality Assessment (DQA) of TB notifications in Zambia: the case of under notification in a national TB program

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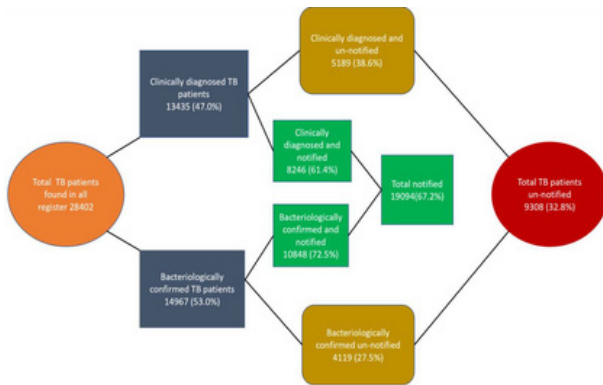
**Background:** Zambia is one of the 30 high TB burden countries globally with 40% of the cases missed. Despite the Country implementing high impact interventions and innovations, the notifications have been declining since 2004.

Findings from DQA in 03 tertiary facilities motivated the TB programme to undertake a countrywide DQA to ascertain and quantify the magnitude of under-notification.

**Design/Methods:** The programme conducted a DQA in 60 high burden districts that contribute at least 94% of the total national notifications. Qualitative and quantitative methods were utilized to collect data for analysis under routine programme conditions targeting all TB patients bacteriologically confirmed and clinically diagnosed between 1st January and 31st August 2019. All forms of TB were included in the assessment.

Comparison of data verified during the DQA against the reported was performed. Statistical significance was used to determine the extent of differences and qualitative data was used to validate or explain these differences.

**Results:** In 265 audited health facilities countrywide, 28,402 TB patients (all forms) were documented among whom only 67% (19,094) were notified. Among the unnotified patients, 44% (4,119) were bacteriologically confirmed. Among the notified TB patients, 56.8% were bacteriologically confirmed while 43.2% were clinically diagnosed for TB with statistically significant association between method of diagnosis and notification ( $p < 0.001$ ). The odds of a bacteriologically confirmed being notified were 1.66 times that of a clinically diagnosed (95% CI: 1.58 to 1.74).



[Figure.]

**Conclusions:** The magnitude of under reporting and under notification is highly significant. This calls for actions to restore the data management system to one that is robust enough to register and report all TB patients being detected and treated. Further, the findings underscore the urgent need to strengthen the linkage to care.

## EP07 Improving TB care in children

### EP07-159-21 Detecting and preventing pediatric TB through systematic household contact investigations in nine sub-Saharan countries

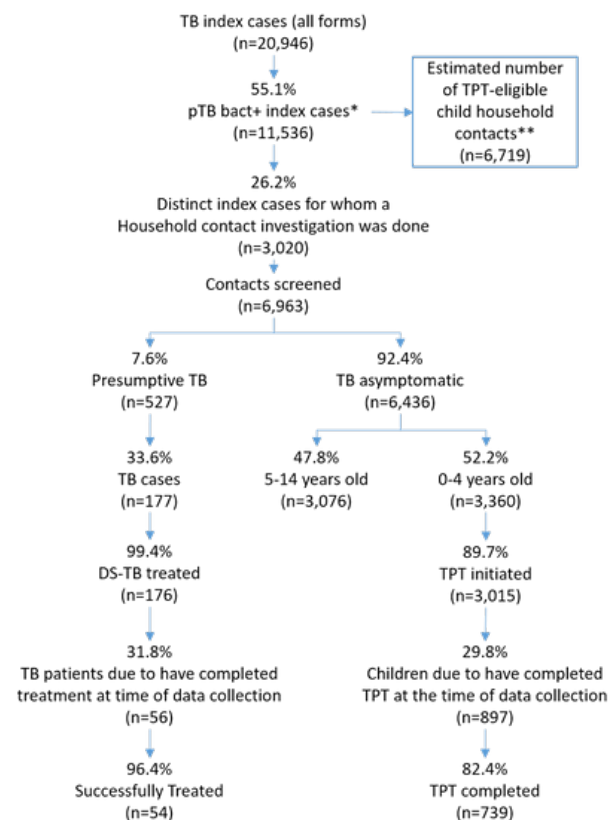
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**Background:** Pediatric TB prevention and diagnosis is challenging, particularly in high TB burden countries. Despite poor implementation, systematic household contact investigation (HCI) remains a key active TB case finding intervention and allows the identification of children eligible for TB preventive therapy (TPT), including children aged 0-4 years who are contacts of TB index cases. We evaluated cascades of care for pediatric TB detection and TPT during systematic HCI. This work informs the scale-up of HCI by documenting both cascade yields.

**Design/Methods:** In 114 health facilities across nine sub-Saharan countries (Cameroon, Côte d'Ivoire, DRC, Kenya, Lesotho, Malawi, Tanzania, Uganda, and Zimbabwe) training and support for health workers, including community health workers, were recruited and

trained to perform HCI (screening children 0-14 years for TB symptoms in households, and identification of TPT eligibility for children under 5 years). Presumptive TB and TPT-eligible children were referred to health facilities for TB investigation or TPT initiation. Data from HCI events performed from December 2018 to December 2019 were collected prospectively using a project form. Proportions were calculated using descriptive statistics.

**Results:** Among 6,963 children screened for TB symptoms at their households, 7.6% (527) were identified as presumptive TB, of which, 33.6% (177) were confirmed and 99.4% (176) were initiated on DS-TB treatment with a 96.4% treatment success rate (54/56). Among 6,436 children without TB symptoms, 52.2% (3,360) were 0-4 years old and eligible for TPT. We successfully linked 3,015 of 3,360 eligible (89.7%) to treatment, with an 82.4% (739/897) TPT completion rate.



\*Estimated from the TB index cases all forms documented by the project and applying the latest WHO reported proportions pTB among TB cases and proportions of bacteriological confirmation (bact+) among pTB cases for each country.

\*\*Calculated using the WHO formula for the estimation of number of child household contacts eligible for LTBI treatment in high TB burden countries.

[Figure.]

**Conclusions:** Systematic HCI is effective for pediatric TB detection and prevention. Both cascades showed good retention between case identification and treatment completion. Systematic HCI offers a unique opportunity to prevent and detect TB among children and should be prioritized.



## EP07-160-21 Pediatric TB detection and treatment cascade in nine sub-Saharan Countries following the CaP-TB intervention

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**Background:** Challenges in pediatric diagnosis translate into an underestimation of childhood TB burden. Treatment outcomes remain poorly documented in children due to a lack of age disaggregation in routine reporting by countries. Careful documentation of the TB detection and treatment cascade helps characterize pediatric TB outcomes and measure gaps in service provision. We evaluated the cascade during the CaP-TB multi-pronged intervention aimed at improving pediatric TB case detection across nine sub-Saharan countries. This work helps characterize the epidemiology of pediatric TB and develop accurate targets for childhood TB programming in this region.

**Design/Methods:** 198 health facilities were purposively selected across Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Kenya, Lesotho, Malawi, Tanzania, Uganda, and Zimbabwe. The selected intervention sites received targeted pediatric-specific TB symptom screening and diagnosis training, increased access to Xpert MTB/RIF testing through strengthened sample collection and transport, and intensified household contact investigation (HCI) for all child contacts (0-14 years) of bacteriologically-confirmed pulmonary TB index cases. Data were collected prospectively from December 2018 to December 2019 using a project form. Proportions were calculated using descriptive statistics.

**Results:** Among 606,443 children screened for TB symptoms, 1.7% (10,027) were identified as presumptive TB, of which, 56.4% (5,660) were tested using Xpert MTB/RIF.

Overall, 25.9% (2,593) of presumptive cases were diagnosed with TB, of which, 22.4% (580) were bacteriologically confirmed, and 98.2% (2,546) initiated on DS-TB treatment. Among those with an expected treatment outcome at the time of analysis, 86.0% (882/1,025) achieved treatment success.

**Conclusions:** Our data demonstrate overall high retention in the childhood TB cascade of care during a childhood-TB specific multi-faceted intervention. One of four presumptive cases was diagnosed with TB, representing a high yield. Although a majority of children were tested with Xpert, most were diagnosed based on clinical and/or radiological findings. HIV status does not influence treatment success.

Number of children screened	606,443
Identified presumptive TB investigated	1.7% (10,027/606,443)
Tested with Xpert	56.4% (5,660/10,027)
TB diagnosis rate (among presumptive TB cases)	25.9% (2,593/10,027)
% bacteriologically confirmed	22.4% (580/2,593)
TB diagnosis rate among HIV+ presumptive TB cases	14.2% (118/829)
Initiated on DS-TB treatment	98.2% (2,546/2,593)
Treatment success (among TB patients due to have completed Tx at time of data collection)	86.0% (882/1,025)
Treatment success among HIV+ individuals (treated for DS-TB and due to have completed Tx at time of data collection)	86.8% (33/38)

[Table. Pediatric TB Detection and Care Cascade]

## EP07-161-21 Increasing pediatric TB detection and treatment in private health sector in India

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**Background:** India's private health sector is vast and unregulated, with significant gaps in diagnosis and notification of Pediatric TB, along with sub-optimal standards of care. The Catalyzing Pediatric TB Innovations (CaP TB) project aims to improve quality of care for Pediatric TB along with integrating TB screening and care among outpatient and in-patient services in private health facilities.

**Design/Methods:** 1,565 private pediatric healthcare facilities were mapped in six districts across Andhra Pradesh, Maharashtra, and Telangana states of India. Of which, 57 were purposively selected based on their case load, service availability, and willingness to provide comprehensive TB services. Selected sites received onsite sensitization, training on pediatric TB management, cost reimbursement of select sample collection procedures, transportation to government supported Xpert MTB/RIF centres, and household contact screening for all TB index cases. Data were collected prospectively from July 2019 to February 2020 using a standard questionnaire, and proportions calculated using descriptive statistics.

**Results:** Among 181,559 children screened for TB symptoms, 0.6% (1,117) presumptive TB were identified. Of presumptive cases, 68% (761) were tested using Xpert

MTB/RIF where 99.9% tested in government centres and 77% (861) with Chest X-ray. Overall, TB was diagnosed in 9.6% (107) of presumptive cases, of which 20.6% (22) were bacteriologically confirmed. Number needed to screen (NNS) to identify a positive case was 1,697. Among the 106 (99%) TB cases initiated on DS-TB treatment, 74% were prescribed government-provided FDC, and 66.6% (10/15) of those with expected outcomes at the time of data collection achieved treatment success. Majority (51%) of pediatric TB cases were 0-4 years old.

**Conclusions:** We demonstrated the feasibility of systematic TB screening integration in the private sector and the optimal use of the government-supported diagnostics and treatment. Challenges included the use of private FDC drugs with sub-optimal dosage, and linkage to appropriate services to ensure continuum of care.

	July 2019-Feb 2020
Number of sites	57 sites
Number of children screened	181,559
Presumptive TB identified out of screened	0.6% (1,117/181,559)
Tested with Xpert	68% (761/1,117)
TB diagnosis rate (among presumptive TB cases)	9.6% (107/1,117)
% bacteriologically confirmed	20.6% (22/107)
Initiated on DS-TB treatment	99% (106/107)
Treatment success (among TB patients due to have completed Tx at time of data collection)	66.6% (10/15)
Number Needed to screen to identify one TB case (NNS)	1,697

[Table 1: Pediatric TB Detection and Care Cascade]

### EP07-162-21 Training physicians in India to interpret pediatric chest radiographs according to World Health Organization research methodology

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**Background:** Chest radiography is the standard for diagnosing pediatric lower respiratory infections in low-income and middle-income countries. A method for in-

terpreting pediatric chest radiographs for research endpoints was recently updated by the World Health Organization (WHO) Chest Radiography in Epidemiological Studies (CRES) project. Research in India required training local physicians to interpret chest radiographs following the WHO method. We described the methodology for training Indian physicians and evaluated the training's effectiveness.

**Design/Methods:** Twenty-nine physicians (15 radiologists and 14 pediatricians) from India were trained by two WHO CRES members over three days in May 2019. Training materials were adapted from WHO CRES resources. Participants followed WHO methodology to interpret 60 chest radiographs during pre- and post-training examinations. Participants needed to correctly classify >80% of radiographs for primary endpoint pneumonia on the post-training test to be certified to interpret research images. We analyzed participant performance on both examinations.

**Results:** Twenty-six of 29 participants (89.7%) completed both examinations. The average score of examinees increased by 9.6% (95% CI, 5.0%, 14.1%) between examinations. Participants correctly classifying >80% of images for primary endpoint pneumonia increased from 69.2% (18/24) on the pre-training to 92.3% (24/26) on the post-training test. We found the mean score of radiologists on the post-training examination was not superior than pediatricians (p=0.43).

**Conclusions:** Our results demonstrate that this training approach utilizing revised WHO CRES definitions and adapted tools was successful. We recommend future research incorporating WHO chest radiograph methodology to consider modelling trainings after this approach.

### EP07-163-21 Care cascade of contact screening and preventive therapy among children under five in high burden districts of Nepal

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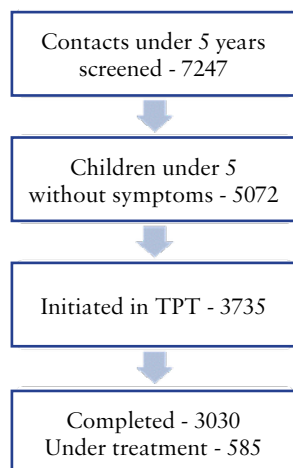
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**Background and challenges to implementation:** In Nepal, childhood tuberculosis was poorly addressed in routine national TB programs (NTP); contact tracing and TB preventive therapy (TPT) were not implemented. NTP in 2017 initiated household contact screening and TPT for children <5 years in 38 high TB burden districts.

**Intervention or response:** Care cascade constructed in this paper focuses on contract tracing done the period of March 2018- Dec 2019, on 38 high TB burden districts of Nepal caring 85% of total TB cases. Symptom screened was done among household members of smear positive pulmonary tuberculosis (PTB) cases, and those screened positives were referred for evaluation. All as-

ymptomatic children < 5 were referred for TPT initiation. Once enrolled in TPT, family member DOT was followed with monthly visit at the health facility. But to ensure treatment compliance and completion health workers also conducted twice household visits to ensure compliance.

**Results/Impact:** Contact tracing of 27,982 PBC TB cases were done in the given period. Total of 14,6562 family members were screened and 5% (7,247) of contacts were under 5 years old. Based on screening 5,072 (70%) were eligible for TPT and 3,735 (73.6%) were initiated in TPT. Among TPT initiated 3,615 (96.8%) were retained in treatment, with 3,030 (83.8%) completing treatment and 585 (16.2%) still under treatment and 120 (3.2%) discontinued. No TB disease was found amongst those initiated in TPT. Only 3.2% discontinued their treatment which can be attributed to the program's focus to ensure completion of treatment through follow-up by health care providers to ensure compliance and transportation cost for monthly pill pickup.



[Figure.]

**Conclusions:** The result has shown that a strong care cascade for preventive therapy can be achieved in a low-resource setting, with apparent immediate impact on TB outcomes. The programme should be scaled-up throughout Nepal, through provision of adequate budget form both government and donors maintaining routine supervision to ensure compliance and completion of TPT.

## EP07-164-21 Pediatric latent tuberculosis infection (LTBI) cascade of care from the TB and Leprosy Free Majuro community mass screening project

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**Background and challenges to implementation:** Describe the implementation and outcomes of mass screening and treatment for LTBI in children 0-14 years old in Majuro, Republic of the Marshall Islands (RMI) during the "TB and Leprosy Free Majuro" project.

**Intervention or response:** TB and Leprosy Free Majuro was implemented by the RMI-Ministry of Health (MOH) on Majuro Atoll from June to November 2018. This project was unique because it offered screening and preventative treatment for children 0-14 years old. The screening algorithm included a symptom inquiry, contact history, and physical exam. Further evaluation included a chest x-ray and sputum collection if algorithm results suggested active TB. A tuberculin skin test (TST) was planted on children  $\geq 5$  years old and considered positive if it was  $\geq 10$  mm, or  $\geq 5$  mm with a known exposure. LTBI treatment was recommended for children 0-4 years if a TB exposure was reported and recommended for children 5-14 years with a positive TST reading.

Age Group (years)	0-4	5-9	10-14	Total
Estimated Majuro Population* *based on 2010 census data	3,950	3,565	3,604	11,119
Initiated screening	1,657	2,812	3,034	7,503
Completed screening, n (% of total population)	1,260 (32%)	2,555 (72%)	2,748 (76%)	6,563 (87%)
Total with TST results or age <5 with TB exposure information	1,085	2,514	2,731	6,330
Positive TST or age <5 with TB exposure, n (%)	120 (11%)	215 (9%)	446 (16%)	781 (12%)
Treatment initiated among TST+ or age <5 with TB exposure, n (%)	33 (28%)	153 (71%)	398 (89%)	584 (75%)
Treatment completed, n (%)	27 (82%)	138 (90%)	348 (87%)	513 (88%)

[Table 1. Pediatric LTBI Cascade of Care, TB and Leprosy Free Majuro, 2018]

**Results/Impact:** 11,119 children were eligible for screening. 7,503 (71%) attended their first appointment and 6,563 (62%) completed screening. 32% of children aged 0-4 years, 72% of children aged 5-9 years, and 76% of children aged 10-14 years completed screening. In the 0-4 year group 154 had a TST reading, 14 (9%) were positive, and 19 children had known exposures. 33 children started LTBI treatment and 27 (82%) completed



it. In the 5-9 year group 2,514 children had a TST reading, 215 (9%) were positive, 153 started LTBI treatment, and 138 (90%) completed it. In the 10-14 year age group 2,731 children had a TST reading, 446 (16%) were positive, 398 started LTBI treatment, and 348 (87%) completed it.

**Conclusions:** A low percentage of children 0-4 years completed screening. Screening completion improved with increasing age cohort. Treatment completion was high across all age cohorts if it was initiated.

### EP07-165-21 Improvement of screening for childhood tuberculosis in Senegal coupled with screening for malnutrition: pilot study in the health districts of Thiès and Tivaouane (Sénégal)

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**Background and challenges to implementation:** Tuberculosis in children is often under diagnosed. The Objective of this study developed with OMS/TDR was to demonstrate that integrating TB screening into the activities carried out by the malnutrition unit (Senegal) are effective (in terms of the number of children diagnosed), feasible and permissible (by parents / guarantors, staff (health region, medical region and programs)

**Intervention or response:** A mixed quantitative and qualitative estimate was done. It was a cross-sectional, mixed intervention pilot study, aimed at assessing the feasibility and acceptability of active screening for TB in children 0-14 years old, coupled with malnutrition screening campaigns in Thiès and Tivaouane taking place over 10 days.

**Results/Impact:** 74 community sites were enrolled, with 26,453 children aged 0-14 being enrolled. The sex ratio was 0.82. Coughing longer than 15 days and malnutrition were the main clinical signs of reference. Malnutrition was diagnosed in 559 children out of 1364 referred to health posts. The X-ray's was carried out in 1065 children (87.3%). Five children were detected to have Tuberculous during this campaign and put on treatment. The campaign was well received. At the community level, the reasons for the positive assessment due to the coupling campaign were numerous, as the campaign was free and it was a means of assessing the state of health of their child. Providers also found this campaign useful, it offered an opportunity to screen children who are often "forgotten" in the management of TB.

The main difficulties listed are the lack of motivation, the difficulties of transporting communities following the referral, problems related to the availability of gastric tubes for children. Most of the respondents believe that this activity should be sustained and extended in their district.

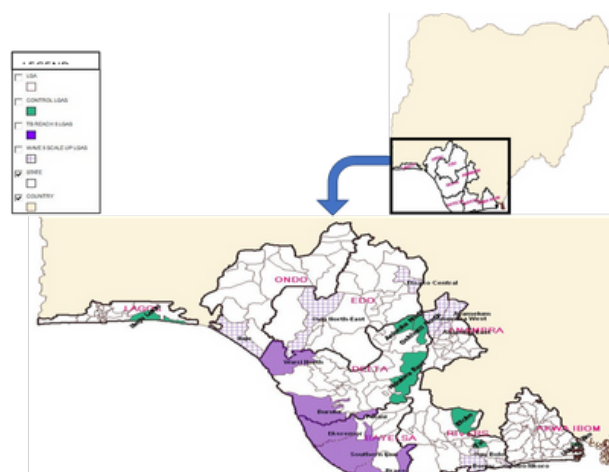
**Conclusions:** This campaign is an opportunity to reach the often overlooked child. Sustainability of this project could reduce the prevalence of Tuberculosis in their district.

### EP07-166-21 Barriers to uptake of Isoniazid Preventive Therapy (IPT) among eligible under 6 child household contacts of tuberculosis patients in Southern Nigeria

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**Background:** Nigeria's National Tuberculosis Control Programme (NTP) guidelines recommend tuberculosis (TB) screening of household contacts (aged <6 years) and IPT for those eligible. We evaluated the uptake of IPT among eligible child contacts of bacteriologically-positive TB patients notified between 2016-2018 and its implementation barriers from the patients' and health-care workers' perspectives.

**Design/Methods:** This is an exploratory mixed-methods study carried-out in six states in Southern Nigeria. The study had a quantitative phase (cross-sectional survey of TB patients and a review of programme records of the study facilities), and qualitative phase (12 focus group discussion with TB patients (n=112) and key informant interviews (n=12) with healthcare workers).



[Figure.]

**Results:** The records of 1244 TB patients were reviewed, 197(15.8%) had children (aged <6 years) in their households. Overall, 176 bacteriologically-positive TB patients (mean age 38.5 years, SD  $\pm$ 13.8; 59.1% male) completed the survey, and 74(42.0%) had under-six child contacts. Participants received education on cough etiquette 155(88.1%) and need for IPT among children 74(42.0%). Only 40.5% (30/74) of the eligible children received IPT. Non-initiation of IPT was significantly more likely among child contacts of an index case if the patients were not told why IPT should be given (RR 1.83; 95% C.I. 1.25–2.66), were not told to bring the children in their household for TB screening (RR 2.0; 95% C.I. 1.36–2.94), and were not told the duration of IPT for children (RR 1.92; 95% C.I. 1.23 – 3.03). Qualitative analysis revealed the following barriers to IPT implementation: poor knowledge of TB, inadequate education by healthcare workers, poor risk perception about IPT, concerns about the adverse effects of isoniazid, costs of care and inadequate staffing.

**Conclusions:** Uptake of IPT among child contacts of TB patients in Nigeria is poor due to several factors. Appropriate context-specific approaches are needed to address the patients and health systems barriers.

### EP07-167-21 The state of paediatric, rifampicin-resistant tuberculosis in Khayelitsha, South Africa

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**Background:** Globally, an estimated 25,000-34,000 (10-15%) paediatric cases (0-14 years) become sick each year due to rifampicin-resistant tuberculosis (RR-TB). The majority are never diagnosed or treated for their disease, and are often denied access to scientific advances; few programmes focus on RR-TB detection and initiation of treatment in paediatric patients. We report on paediatric RR-TB diagnosis and treatment in a decentralised setting in Cape Town.

**Design/Methods:** This retrospective analysis included paediatrics (0-14 years) diagnosed with RR-TB from 2012–2017 in Khayelitsha. We report on the number diagnosed, started on treatment, and final treatment outcomes.

**Results:** Overall, 1,230 cases of RR-TB were detected in Khayelitsha from 2012-2017, of which 63 (5%) were paediatric cases. Overall, 62%, 16%, and 22% of patients were <5, 5-9, and 10-14 years of age, respectively. Thirty-two (51%) patients did not have bacteriological

confirmation, but were initiated on treatment based on clinical diagnosis and contact history; 25% had confirmed multidrug-resistant TB; 9% had RR-TB diagnosed on GeneXpert without further microbiological results; 11% had rifampicin monoresistant TB; 4% had RR-TB with additional fluoroquinolone resistance. Fifty-five (87%) initiated RR-TB treatment, the majority (62%) in hospital. Treatment outcomes were as follows: 84% treatment success, 4% lost to follow-up, 2% treatment failure, 5% treatment stopped, and 5% not evaluated. Eight children with bacteriologically confirmed RR-TB did not start second-line TB treatment; one initiated drug-sensitive TB treatment and the remainder were not found when recalled.

**Conclusions:** Outcomes for paediatrics who receive treatment for RR-TB are excellent. Despite universal access to Xpert MTB/RIF in South Africa since 2011, the frequency of paediatric cases detected has not increased, suggesting that diagnosis of RR-TB in paediatrics remains a challenge. Further efforts for improving case detection, contact assessments, and appropriate treatment initiation, particularly among those with bacteriologically confirmed disease, are urgently needed for this vulnerable population.

### EP08 COVID-19 and TB: friends or foes?

#### EP08-168-21 Tuberculosis and Covid-19: Bangladesh Perspective and challenges

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**Background and challenges to implementation:** Despite many challenges, countrywide coverage, increasing trend of notification and sustained treatment success, were the key features of TB control in Bangladesh, implemented by Government and NGOs. The novel Covid-19 pandemic posed challenges in TB control in this high TB burden country with a population of 160 million. COVID-19 started in March, 2020 and showed a rising trend. Government declared a lockdown in late March. A total 14,657 COVID-19 confirmed cases and 228 deaths were reported by May 10, 2020. Changes in modalities in TB implementation during the pandemic were explored.

**Intervention or response:** Reviewed programme data, interim guidelines, policies, and implementation modalities for TB, in the first two months of the pandemic. New modalities were adopted due to widespread “stay home” order. Although all TB diagnostic centers were open, ac-

tive case finding was hampered due to restriction. Hospital attendance reduced for all diseases including TB. Patient centered care were ensured by providing medicine for long to the patient. Telecommunication were established for follow up and to conduct patient education on COVID-19. Uninterrupted supply of medicine were ensured. TB staffs were trained on COVID-19 and infection prevention.

**Results/Impact:** A decrease in TB patients are reported by partners, (21257 and 5015 in March and April, respectively). TB patients from low income group were vulnerable to further poverty. Telecommunication used and ensured the continuity of care for ongoing patients. A number of Medical workers have been diagnosed with COVID-19 in Bangladesh, including 10 TB staff. Infection prevention of the front liners remain a challenge as the symptoms are related.

**Conclusions:** COVID-19 Pandemic challenged the TB control effort. Interim and long term preparedness is required to ensure effective TB services and resume the enhanced momentum of TB control. Limited testing capacity, irregular lockdown policies, and inadequate find-isolate treat approach are the main challenges for COVID-19.

### EP08-169-21 The impact of Covid-19 on tuberculosis control in Coast General Teaching and Referral Hospital in Mombasa County, Kenya

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**Background:** The Global COVID-19 pandemic started in November 2019. Kenya confirmed its first case on 12th March 2020. Mombasa County is the second highest TB burden county in Kenya, 3,731 TB cases were reported last year 2019. Coast General Teaching and referral hospital (CTRH) contributes the highest number 491 (13%) of TB case in the county.

**Design/Methods:** Reviewed service delivery data for the period between 1st March 2020 and 30th April 2020 and similar period last year 2019. Data was extracted from the primary source documents and entered in excel sheet. Data analysis was conducted using excel and comparison was made on number of samples processed in these two similar periods, number diagnosed with TB and number of patients that were started treatment in the same period. Analysed was also TB cases that were due for follow up smear microscopy at second month, fifth month and sixth month.

**Results:** In the period between 1st March to 30th April 2019, a total of 1,446 GeneXpert samples were processed where in 164 (11%) were positive. In a similar period in 2020 there was a decrease of 601 (42%) in number of GeneXpert samples processed with a high positivity rate

of 15%. There was a decrease of 43% in the year 2020 compared to same period in 2019 on patients initiated TB treatment. Similarly there was significant reduction in follow up smears 22%, 15% and 8% for patients that were due for follow up smears at month two, five and six respectively.

**Conclusions:** The changes introduced to combat COVID-19 are a major barrier to patients with TB symptoms seeking health care, with an inevitable delay in diagnostics and compromised quality of care. However, patients with obvious TB symptoms are seeking care and accessing TB services as shown by positivity rate of 15% in the period under review.

### EP08-170-21 Design and organization of temporary ICU ward in response to the COVID-19 pandemic

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**Background and challenges to implementation:** COVID-19 placed a heavy burden on medical services. For the critically severe patients, ICU wards were insufficient. Here we share our experience of designing and organizing a temporary ICU ward within 48 hours.

**Intervention or response:** COVID-19 is an acute respiratory infectious disease, thus the most important goal of the ward was to prevent the nosocomial transmission. The ICU ward was separated into 3 areas: the buffer area, the contaminated area and clean area. Medical staff and patients used different corridors. Separate rooms for staff preparation, as well as storerooms for sterile resources were created and supervised by head nurses.

As there were limited time and resources to rebuild the ward, to maintain negative pressure in contaminated areas, high-powered exhaust fans were installed in each patient room and used 24 hours per day. The air flowed from clean areas to polluted areas in one direction only.

The use of the central air conditioning system was strictly forbidden. For patient's care, we developed a flow chart for patient admission and created a remote monitoring system in the buffer area for blue codes. We also developed a checklist for staff to check their PPE and an head nurse was assigned to perform a final check.

To prevent burn-out, staffs were limited to work four hours per day in contaminated areas. Staffs were monitored for signs of COVID-19 infection each day and their temperatures were taken twice per day.

**Results/Impact:** A 32-bed ICU ward was established in 48 hours. In two months, 109 COVID-19 patients were admitted. No nosocomial transmission was detected in medical staff.

**Conclusions:** The shortage of beds for critically ill patients with COVID-19 was solved by developing a temporary ICU ward. The space design, environmental cleaning, patient's daily care were the key steps to organize a practical ICU ward during the COVID-19 pandemic.

### EP08-171-21 Trend analysis of exponential increase of Covid-19 cases in Pakistan

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**Background:** The 2019 novel coronavirus (SARS-COV-2) originated in the central Chinese city, Wuhan by end of December 2019. Pakistan reported its first 2 confirmed cases, on 26th February 2020 linked to travel history of Iran. The study was conducted to see the trend of covid infection growth and doubling time in Pakistan from an early containment state to much belated exponential rise.

**Design/Methods:** This study is based on analysis of the available data on COVID-19 from Ministry of National Health Services Regulations and Coordination covid-19 dashboard and National Institute Health Islamabad (NIH) Emergency operation cell (EOC) situation reports from 26th February - 26th April 2020 to see the trends and pattern of covid-19 among Pakistani population.

**Results:** A total of 11,940 COVID-19 patients has been reported with 237 deaths, 111 critically ill and 2527 recoveries. Punjab has highest number of confirmed cases (4767) Sindh (3671), Khyber Pakhtunkhwa (1541), Baluchistan (607) Gilgit Baltistan (300), Islamabad Capital territory (214) Azad Jammu Kashmir (55). Majority of effected patients are male (79.4%). Iran Zairian are making 13% of positive patents. Local transmission cases stand at 79%. Daily cases surge is 5.8% increase per day. 20th April 2020 witnessing highest reported cases and deaths per day so far (796 new Cases and 22 deaths). Pakistan reached its first 100 confirmed cases on 16th March, 2020, 20 days after first reported case. The case doubling time was 3 days initially after first cases then it was reported as seven days and then ten days till 21th April, 2020.

**Conclusions:** Grave mishandling, lack of quarantine facility and limited testing capacity at Taftan border crossing resulted in importation of virus in country. Cumulative confirmed case count in Pakistan is now showing an exponential growth pattern within two months

of start of outbreak. Risk mitigation measures such as lock down by provinces and Federal government being implemented were eased in mid-April due to economic impact. Pakistan with limited testing capacity of 5000-6000 tests per day needs to ramp up testing regime to halt the community transmission leading to exponential increase in cases.

### EP08-172-21 Sustaining TB services during COVID19 pandemic: experience and lessons learnt from Nigeria in 2020

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**Background and challenges to implementation:** Nigeria has the highest TB burden in Africa and is one of the countries affected by the pandemic of coronavirus disease 2019(COVID 19) with 4,399 confirmed cases and 143 death(at 11th May 2020). Measures in place to control COVID 19 create challenges for implementation of TB control activities. The lockdown started on 26th March 2020, it impacted on free movement and provision of TB services. Sustaining TB programme in COVID 19 pandemic become a priority of the TB programme, steps for doing this was documented and described in this study.

**Intervention or response:** TB programme in anticipation of the lock down developed SOP for sustaining TB services during COVID19 pandemic, which describe actions by National, State and LGA levels in ensuring uninterrupted supply of cartridges,consumables and anti-TB medicines to health facilities and patients. Electronic virtual platforms were established for periodic meetings at all levels. Plan for using GeneXpert platform for COVID19 testing developed; weekly GeneXpert machines utilization tracked. SOP for implementing outreaches and integration of TB into COVID19 outreaches during phase relaxation of the lock down developed.

**Results/Impact:** Resources mobilized from COVID19 interventions for strengthening GeneXpert laboratories and for improving biosafety level in selected laboratories. The number of Xpert machines performing optimal number of tests decreased from 58 in the week of 16th March before the lockdown to 22 in the week of 6th April(one week after the lockdown) and gradually increased with the implementation of the SOPs to 31 in the week of 4th May. No stock out of medicines. The use of virtual meetings enhance coordination and communications during pandemic.

**Conclusions:** Effective engagement of stakeholders during the COVID19 pandemic led to mobilization of additional resources to TB programme, early prepara-

tion and effective guidance ensure sustainability of the programme during the pandemic. Video Observed Therapy (VOT) should be strengthened to effectively monitor patients on treatment.

### EP08-175-21 Psychological experiences of Mobile Van TB Screening Team during COVID 19 pandemic in Blantyre, Malawi

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**Background:** Malawi started registering corona virus disease (COVID-19) cases on 2 April 2020 with 56 cases and 3 confirmed deaths reported to date. During the crisis all essential health services are operational including Mobile Van TB Diagnostic Units (MDU) screening services. The MDU services involve screening individuals for TB using X-ray, Gene Xpert and symptomatic screening (cough, fever, night sweats and weight loss). Studies have shown that presenting symptoms such as cough, fever and difficulty breathing are similar in COVID-19 and TB. The study sought to explore psychological experiences of Mobile Van TB Screening team during COVID 19 pandemic.

**Design/Methods:** Qualitative study using an empirical phenomenological approach. A purposeful sampling method was used. A total of 10 health workers were enrolled for the interview (nurses, clinicians, radiographer, laboratory technicians) who provide screening services at Mobile Van TB Diagnostic from 8 April to 30 May 2020. The interviews were conducted face-to-face, transcribed by verbatim and analyzed using Colaizzi's 7-step method.

**Results:** Three themes emerged. Firstly, discomfort and helplessness was caused by fear of being infected with COVID 19 as increased number of individuals who seek MDU services present with similar symptoms as COVID 19. Secondly, stigma and discrimination such as avoided by the community, MDU health workers being on the front line facing the pandemic with COVID 19, community perceived them as a potential source of COVID 19 infection. Thirdly, MDU team members were exhausted with a list of protocols to follow in prevention of COVID 19 such as social distancing which compromised TB screening services.

**Conclusions:** Results have shown that health workers working under MDU experience several psychological challenges in this era of COVID 19 pandemic and have compromised the TB screening services. Therefore, mental health interventions are needed to mitigate these challenges. Self-coping style is important for health workers to maintain mental health.

### EP09 Improved acceptability of TB regimens needed

#### EP09-176-21 Risk factors for cycloserine neurotoxicity in patients treated for multidrug-resistant tuberculosis

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**Background:** Cycloserine is associated with neurotoxicity (psychosis, depression, and neuropathy) but there are limited prospective data of the incidence and risk factors for neurotoxicity in patients on MDR-TB treatment.

**Design/Methods:** We conducted a prospective cohort study of inpatients with MDR-TB in Cape Town and followed them up for 3 months. The treatment regimen included pyrazinamide, moxifloxacin, kanamycin, cycloserine dosed as terizidone, ethambutol, and ethionamide/isoniazid. We assessed peripheral neuropathy using the Brief Peripheral Neuropathy Screen (BPNS), depression using the Kessler-10 (K-10) scale and psychosis using the Brief Psychiatric Rating Scale (BPRS). We defined neuropathy as a worsening of the BPNS symptom score by  $\geq 2$ , and psychosis and depression as BPRS and K-10 scores of  $\geq 32$  and  $\geq 20$  respectively. Cox proportional hazard modelling was performed to explore variables associated with neurotoxicity: HIV status, age, prior TB treatment, alcohol use, isoniazid/ethionamide use, and cycloserine area under the concentration-time curve to 10 hours ( $AUC_{0-10}$ ).

**Results:** Data were available for 144 participants: 78 men; median age 35.2 years; 89 (62%) HIV-positive; 105 (73%) had prior TB treatment. The cycloserine median  $AUC_{0-10}$  was 597.2  $\mu\text{gh/mL}$ . Fifty participants (35%, 25 cases per 100 observation months) were diagnosed with incident or worsening neuropathy, 14 (10%) with depression, and 11 (8%) with psychosis. No variables were associated with psychosis or depression. Cycloserine  $AUC_{0-10}$  was associated with neuropathy (HR: 1.08 per 100 unit cycloserine  $AUC_{0-10}$  increase;  $p: 0.037$ ) on univariate analysis, but the association lost significance after adjusting for HIV status and age (aHR: 1.04,  $p: 0.323$ ). Age was independently associated with neuropathy (aHR: 1.37 per 10 year increase;  $p: 0.044$ ).

**Conclusions:** We describe high incidence of early neurotoxicity in patients treated with cycloserine for MDR-TB. Cycloserine exposure was associated with incident or worsening peripheral neuropathy, but not with psychosis or depression, in unadjusted analyses.

	HR (95% CI)	p value	aHR (95% CI)	p value
HIV	1.85 (0.99 to 4.43)	0.053	1.98 (1.00 to 3.91)	0.050
Age (per 10 yr increase)	1.24 (0.95 to 1.62)	0.110	1.37 (1.00 to 1.86)	0.044
Previous TB treatment	1.59 (0.77 to 3.27)	0.210		
Alcohol	1.50 (0.81 to 2.71)	0.200		
Ethionamide use, n=120	1.41 (0.64 to 3.15)	0.395		
Isoniazid use, n=121	0.69 (0.33 to 1.41)	0.305		
Cycloserine AUC <sub>0-10</sub> (per 100 unit increase)	1.08 (1.00 – 1.17)	0.037	1.04 (0.96 to 1.13)	0.323
Cycloserine C <sub>max</sub>	1.02 (1.00 to 1.04)	0.020		

[Table. Covariates associated with incident or worsening peripheral neuropathy in patients treated with terizidone for multidrug-resistant tuberculosis]

### EP09-177-21 Hearing loss on second line injectable therapy for rifampin resistant tuberculosis in a retrospective cohort in Worcester, South Africa

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**Background:** Second-line injectables (SLIs) have long served as core drugs in rifampin resistant tuberculosis (RR-TB) regimens. Despite their recent WHO Group C classification, SLIs are still mainstays in many settings.

**Design/Methods:** We conducted a retrospective cohort study of all RR-TB patients at Brewelskloof Hospital, Worcester, South Africa from 12/2015-6/2017. During the study period, an 18–24-month RR-TB regimen was administered with SLI for the initial 6–8 months. SLI dosing was reduced to 3 times per week or changed to bedaquiline (BDQ) if moderate-severe hearing loss was

identified on audiometry. We compared baseline characteristics between patients who tolerated full strength SLI and those requiring dose reduction or switch to BDQ using Pearson chi-squared, Fisher's exact, and Student t-tests.

**Results:** Fifteen patients were excluded from the analysis due to regimen adjustments for reasons other than hearing loss (5 due to SLI resistance and 10 due to renal insufficiency). Of 104 RR-TB patients included, 62.5% were HIV positive, 78.6% had a previous TB history, 27.9% tolerated the SLI for the full therapy duration, and 72.1% had a regimen adjustment due to hearing loss. Those requiring a regimen adjustment trended to being older (40.4 vs 36.6, p=0.10) and having HIV (66.7% vs 51.7%, p=0.16, Table 1).

**Conclusions:** We showed no significant association between SLIs induced hearing loss and HIV, older age, or previous TB. The WHO recommends assessment for ototoxicity during SLI use, however this is not readily available in many settings. Our data suggest that it is not possible to predict who may develop hearing loss, making it difficult to risk stratify patients to more expensive SLI-sparing regimens based on SLI-induced ototoxicity risk.

N (%) or mean (SD)	No Hearing Loss (N=29, 27.9%)	Hearing Loss (N=75, 72.1%)	Overall (N= 104)	p value
Age (years) (N=103)	36.6 (9.4)	40.4 (10.6)	39.4 (10.4)	0.101
Female	16 (55.2%)	34 (45.3%)	50 (48.1)	0.368
Body Mass Index (N=94)	18.9 (4.9)	18.6 (3.3)	18.6 (3.8)	0.761
Currently employed (N=102)	6 (20.7%)	24 (32.9%)	30 (29.4%)	0.223
HIV positive	15 (51.7%)	50 (66.7%)	65 (62.5%)	0.158
Any history of TB (N=103)	21 (75.0%)	60 (80.0%)	81 (78.6%)	0.582
Extra-pulmonary TB (N=79)	1 (4.8%)	8 (13.8%)	9 (11.4%)	0.432
Tobacco Use	22 (75.9%)	47 (62.7%)	69 (66.4%)	0.202
Alcohol or illicit drug use	18 (62.1%)	43 (57.3%)	61 (58.7%)	0.660

[Table 1: Participant Demographics Stratified by Tuberculosis (TB) Second Line Injectable Therapy Attributed Hearing Loss Status]

### EP09-178-21 Treatment outcome of shorter regimen for multi drug resistant tuberculosis in Pakistan 2018

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**Background and challenges to implementation:** In 2016, WHO recommended shorter regimen for patients who have not been previously treated for more than one month with second-line medicines used in the shorter MDR regimen or in whom resistance to fluoroquino-

lones and second-line injectable agents has been excluded. National TB control Programme, Pakistan recommended shorter regimen with duration of 9-11 months in January 2018 under programmatic settings in all PMDT site of country.

**Intervention or response:** All patients were assessed for shorter regimen at the time of enrollment. Patient who have exposure or resistance to any second line drug used in shorter regimen were put on longer regimen. Patients with extra pulmonary TB and extensive parenchymal disease and who did not provided consent were also excluded from shorter regimen and put on longer regimen.

We compared treatment outcome of patients who were put on shorter regimen with those who were eligible for shorter regimen but put on longer regimen and whose outcome are known. Data was collected from all PMDT sites of Punjab and Khyber-Pakhtunkhwa.

**Results/Impact:** A total of 723 patients were put on shorter regimen and 1124 patients were put on longer regimen. The treatment outcome of the patients put on shorter regimen were significantly better than patient put on longer regimen (treatment success rate 74% vs 67%). Similarly cure rate was better in shorter regimen than longer (71% vs 64%). Death was higher in patients who were put on longer regimen (18%) compared to shorter regimen (10%). Lost to follow-up was slightly higher in shorter regimen (10% vs 8%). Treatment failure was same in both cohorts (2%).

**Conclusions:** In patients with no history or resistance to second line drugs, a 9-11-month shorter regimen has better outcomes compared to longer regimen.

### EP09-179-21 From pilot to nationwide scale up of shorter treatment regimen for DR-TB treatment: lessons from Nigeria

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**Background and challenges to implementation:** At inception of Challenge TB (CTB) project in 2015, only 4 DR-TB treatment facilities across 12 states of geographical coverage. Following adoption and rapid scale-up of GeneXpert as primary TB diagnostic tool, limited bed spaces resulted in challenges of huge number of diagnosed DR-TB patients on treatment waiting lists.

**Intervention or response:** The CTB project with National TB and Leprosy Control Program (NTBLCP) and other partners, established 43 decentralized DR-TB out

patient's department clinics (OPD) across 12 geographical coverage areas. By 2016 CTB project and partners facilitated implementation of shorter treatment regimens and new drugs (STR & NDs) of 9 – 11 months duration, including active drug safety monitoring and management (aDSM) to ensure DR-TB patients' adherence and treatment completion through capacity building of 390 national and state DR-TB teams, 862 clinicians and health care workers as well as review and distribution of guidelines, SOPs and national recording & reporting tools.

**Results/Impact:** Through the decentralized approach to DR-TB treatment across 12 CTB geographical coverage areas, number of DR-TB patients steadily increased from 849 DR-TB patients in 2016 to 1,226 in 2019 (a cumulative total of 4,168 patients). At close of CTB project in 2019, DR-TB patients' treatment enrollment improved from 57% in 2016 to 87% in 2019; while patients initiated on treatment in the community at decentralized OPD clinics improved from 61% in 2018 to 76% in 2019.

Across the country, NTBLCP from 2017 to 2018 recorded increase of Patients successfully enrolled on STR (325 to 1,784); while interim treatment outcomes at 6 months for patients enrolled on STR increased from 63% in 2017 to 79% in 2018.

**Conclusions:** Pilot and national scale up of shorter treatment regimen contributed to increased enrolment and improved interim treatment outcome for DR-TB patients. The NTBLCP and partners should embrace novel treatment regimen to further improve on these achievements.

### EP09-180-21 Preferences for shorter regimens and child-friendly formulations for TB preventive treatment among families affected by TB in Lima, Peru

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**Background:** TB preventive treatment is a critical component of TB elimination. When building capacity for preventive treatment, is important for programs to consider factors that make it easier for patients to complete treatment. We sought to determine what preventive treatment regimens household contacts of patients with TB in Peru would prefer, and to understand the drivers behind their preferences.

**Design/Methods:** We conducted a qualitative research study using a framework analysis approach. We held three focus group discussions with 16 members of fami-

lies affected by TB in Lima, Peru. First, participants were asked to vote for one of four WHO-recommended regimens for drug-susceptible TB preventive treatment that they would prefer for themselves or their children. Next, a focus group was conducted to discuss their reasons for their selected regimen. Coding initially followed a deductive approach based on prior research, with data-driven codes added during the process.

**Results:** In total, 7 (44%) participants voted for 3 months isoniazid and rifapentine (3HP), 4 (25%) chose 3 months isoniazid and rifampicin (3HR), 3 (19%) chose 4 months rifampicin (4R), and 2 (13%) chose 6 months isoniazid (6H). Preferences for shorter regimens were driven by concerns over “getting tired” or “getting bored” of taking medications over time, the difficulty of remembering to take medications, side effects, and interference with daily life. For some, these concerns led to a preference for 3HP because the weekly dosing was perceived as being easier to remember and less disruptive. However, among caregivers, the predominant driver of regimen choice was palatability, and having a child-friendly formulation was more important than regimen duration.

**Conclusions:** There is demand for shorter regimens and child-friendly formulations for preventive treatment in high-burden settings. People have different preferences and priorities, suggesting that having multiple treatment options available could help support patient-centered care and treatment success.

### EP09-182-21 Safety and efficacy of allogeneic $\gamma\delta$ T cells for MDR-TB: an interim analysis of a prospective single-center open-labeled non-randomized controlled matched trial

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**Background:** New MDR-TB treatment strategies are required.  $\gamma\delta$ T cells are essential in tuberculosis immune response, and our pilot study indicated its potential for treating MDR-TB (NCT03575299).

**Design/Methods:** For the control, linezolid/moxifloxacin/cycloserine/clofazimine/pyrazinamide is used for nine months. If fluoroquinolone-resistance or pyra-

zinamide-resistance is detected by MIC or WGS, prothionamide, pyrazinamide, and high-dose INH will be the substitute, with course extended to 12 months. For the experiment, allogeneic  $\gamma\delta$ T cells is added every two weeks, 12 times in 6 months.

**Results:** Till now, 12 patients were enrolled in the experiment group, and 12 patients were extracted from an MDR-TB cohort to match, with four fluoroquinolone-resistant cases in each group. In the experiment, four patients are still on treatment; eight patients had completed the treatment (9-12 months) and a 3-month follow-up, 100.0% (8/8) were cured and had no relapse; In the control, 100.0% (10/10) were cured and had no relapse. In the experiment, 83.3% (10/12) had a positive baseline culture, and 70.0% (7/10) experienced culture conversion within two months and 90.0% (9/10) within six months and 100% (10/10) within eight months; In the control, 83.3% (10/12) within two months and 100.0% (12/12) within six months. In the experiment arm, allogeneic  $\gamma\delta$ T cells were given for 136 times, and two patients reported mild short fever for once. In the experiment, some drugs held responsible for serious AEs were discontinued: clofazimine in 8.3% (1/12, due to QT prolongation) and cycloserine in 8.3% (psychiatric) of patients. In the control: linezolid in 16.7% (8.3%, 1/12, due to myelosuppression; 8.3%, neuropathy) and moxifloxacin in 8.3% (Achilles tendon pain) and cycloserine in 16.7% (psychiatric) of patients.

	cure	Culture conversion within two months (%)	Culture conversion within six months (%)
$\gamma\delta$ T cells	100.0% (8/8)	70.0% (7/10)	90.0% (9/10)
Control	100.0% (10/10)	83.3% (10/12)	100.0% (12/12)

[Table]

**Conclusions:** MDR-TB patients using allogeneic  $\gamma\delta$ T cells and all-oral short-course regimen experienced high culture conversion within two and six months and high cure rate and no relapse. The toxic effects of allogeneic  $\gamma\delta$ T cells and drugs were manageable.



### EP09-183-21 Interim outcomes of bedaquiline-containing regimen for the treatment of MDR/ XDR-TB: a prospective cohort study from Hunan, China

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**Background:** China introduced bedaquiline relatively late and few data exist on its use outside clinical trials. The purpose of this study was to evaluate the effectiveness and safety of bedaquiline-containing regimen for 24-week intensive treatment of multidrug drug-resistant tuberculosis and extensively drug-resistant tuberculosis (MDR/XDR-TB) in Hunan province, China.

**Design/Methods:** A prospective cohort study was conducted on MDR/XDR-TB patients enrolled with bedaquiline-containing regimen from March 2018 to September 2019 in Changsha Central Hospital, affiliated to University of South China, interim outcome was analyzed.



[Figure 1. Representative radiologic findings. Computed tomography images of the chest in a 32-year old male with extensive drug-resistant tuberculosis (XDR-TB). The radiologic findings of the male were followed from the beginning of the bedaquiline treatment to the 24 weeks of the treatment. He was diagnosed with pulmonary TB 1 year ago; with a cough, sputum expectoration, fever and haemoptysis. After the diagnosis, he was given first-line anti-tb drugs. However, the symptoms were not relieved and the sputum smears remained positive. The drug susceptibility tests confirmed CDR-TB. He was enrolled to the bedaquiline therapy group. His anti-TB treatment regimen consisted of: moxifloxacin, linezolid, clofazimine, cycloserine, prothionamide, pyrazinamide. A cavity of 4.6cm x 2.9cm was observed in the right lower lobe of the lung prior to the study (a). After 12 weeks of treatment the cavity shrank obviously (b). In week 24 of treatment the cavity closed.]

**Results:** A total of 69 culture-confirmed MDR/XDR-TB patients enrolled, of which 10 (14.4%) were XDR-TB. 63 (91.3%) patients completed 24 weeks of bedaquiline treatment, 29(46.0%) out of 63 patients had positive culture sputum at the initiation of bedaquiline treatment, culture conversion ratios were 75.9% (22 of 29), 93.1% (27 of 29), 100.0% (29 of 29) and 93.1% (27 of 29 after 4, 8, 12 and 24 weeks of initiation of bedaquiline treatment respectively, the median time to conversion was 24 days (interquartile range [IQR]: 14–61 days). Among 52 cases with lung cavities, 48 92.3% completed 24 weeks

treatment, and cavity closure ratios were 37.5% and 64.5% by the end of the 12 and 24 weeks respectively. Of the 69 patients, two patients died (one died of cardiac arrest, and the other died of respiratory failure), three transfer out, one case lost to follow-up, and sputum bacteria reversion occurred in two patients. Three patients developed a transient QTcF > 500 millisecond and one patient experienced frequent ventricular premature beat.

**Conclusions:** Compared to conventional empirical treatment, bedaquiline combined with optimized background regimen has the potential to achieve higher culture conversion and cavity closure at 24 weeks with an acceptable safety and tolerability profile in patients with MDR/XDR-TB in Hunan, China.

### EP09-184-21 Treatment interruption patterns among patients on bedaquiline containing regimen under programmatic conditions

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**Background:** Limited data is available on reasons for treatment interruption among drug-resistant tuberculosis patients on bedaquiline containing regimes.

**Design/Methods:** This pilot exploratory observational study included 275 consecutively enrolled patients who received bedaquiline containing regimen under Programmatic Management of Drug Resistant Tuberculosis in India.

The study aimed to analyse the reasons for interruptions of treatment and loss to follow up (LTFU) during the first six months of treatment. Interruption of  $\leq 30$  days was defined as temporary interruption. Permanent interruption included those where one or more drugs were not restarted. LTFU included those where the treatment regimen was discontinued for more than one month.

**Results:** Among 275 patients with median age of 25 years, 86 (31.3%) patients had at least one interruption with 122 total episodes of interruption; 70 were temporary interruptions, 35 were permanent interruption and 17 were LTFU. The adverse events (AEs) due to drugs were the commonest reason observed in 81.4% of temporary interruption group and 97.1% of permanent interruption group. Personal factors like busy schedule, lack of family support and no improvement with treatment were the commonest reason observed in 94.1% of LTFU group. The provider and environmental related factors were not observed in any interruption episode. QTcF prolongation and nervous system related AEs were most common AEs in temporary and permanent interruption group respectively. The most common temporarily interrupted drug was Bedaquiline and perma-

nently stopped drug was Linezolid. The successful interim outcome among non-interrupters and interrupters at the end of 6 months of treatment were 86.8% and 81.2% respectively ( $p=0.26$ ).

**Conclusions:** Our study observed that drug related AEs are important risk factors associated with treatment interruption. Bedaquiline is the most common drug associated with temporary interruption. Linezolid may lead to permanent interruption. It is important to identify AEs earlier and manage them appropriately to improve the treatment outcomes.

### EP09-185-21 Incidence rate of linezolid adverse events among Myanmar adult MDR/RR-TB patients on individualized longer DR-TB regimens

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**Background:** WHO classified linezolid as Group A drug in 2018 and its use is anticipated to increase after WHO rapid communication (2019). There are evidences about significant treatment success by using linezolid in the MDR/RR-TB treatment. However, it is also associated with common serious, duration and dose-dependent adverse events such as myelosuppression and peripheral neuropathy. The objective of this study was to characterize the safety of linezolid among Myanmar adult MDR/RR-TB patients.

**Design/Methods:** Prospective observational study was conducted of adult MDR/RR-TB patients enrolled in Aung San TB Specialty Hospital, Yangon, Myanmar from January 2017 to March 2018. Study period was from January 2017 to April 2020 to follow till treatment completion of the last enrolled patient. Patients' data were collected from standardized treatment cards for aDSM as well as from hospital in-patient charts. Data were entered in excel and analyzed by SPSS V20. The primary end of the study was linezolid related adverse events, and cases without events were censored when treatment outcomes were declared.

**Results:** Among 47 study participants, 68% were male, median [IQR] age was 37 [25-48] years, HIV positive (19%), diabetes mellitus (19%), BMI <16 (36%) and XDR-TB (45%). Treatment success rate was 64% (30/47). Multivariate analysis by logistic regression showed no statistically significant association between linezolid adverse event and un-successful treatment outcomes. Twenty-two patients had linezolid related adverse events over 45 person-year at risk (49/100-person

years 95% CI: 29-69). Kaplan-Meier plot showed event free probabilities as 58% at one year. Eleven anaemia, 1 leukopenia, 7 peripheral neuropathies, 1 optic neuropathy and 2 anaemia and peripheral neuropathy cases were either stopped linezolid or reduced dose. Fifty percent of anaemia events were grade 3 or 4.

**Conclusions:** Linezolid adverse events were frequent among Myanmar adult MDR/RR-TB patients and aDSM mechanism must be sustained for patients' safety when new regimens are rolled out.

### EP09-186-21 Real time payment of Nikshay Poshan Yojana under Direct Benefit Transfer scheme improved overall notification, treatment-adherence and outcome of TB & DRTB patients in Odisha, India

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**Background and challenges to implementation:** Tuberculosis is one-of-the-top-ten causes of illness, death and disability worldwide. TB-&-DRTB is the-leading-cause of death from a-curable-infectious-disease in India where most patients encounter nutritional-deficiency and lasting-financial barriers to-access-to-treatment, and struggle for continuity and successful-completion. Poverty and undernutrition are few-key-causes and consequences-of-low-notification and poor-adherence among-most-TB-patients in Odisha which faces-huge-challenge of poor-treatment-compliance and adverse-outcome. NPY-thru-DBT is a major-initiative by-the-NTP where benefits are directly-transferred into-the-bank-accounts-of-the-TB-patients thru a-web-based online-transaction-system.

**Intervention or response:** Considering food-assistance as a potentially-influential-means for increasing-notification and adherence-to TB-&-DRTB treatment that-reduces the-costs-to-patients of staying-in-treatment, and for improving-nutritional-status as guided-by WHO's policy-on-nutritional-care-and-support and End-TB-Strategy's emphasis on integrated-patient-centred-care for management-of-comorbidities, NTP, by an-official-order, introduced-DBT in-Odisha in-April-2018.

NTP staff-of-all 31 districts were provided-on-site-training and handholding-support to-ensure-opening bank-accounts and validating-them-with-PFMS for all-treated-TB-patients in-the-state by-three dedicated-PFMS-Consultants. Each notified-TB/DRTB-patient was provided @₹500 as-NPY-support for every-treatment-month (28-days) until-completion. The mechanism was closely-supervised and monitored by-the TB-Unit-

Supervisors, District-TB-Officers, State-TB-Supervisors and the-Central-TB-Division on-daily, weekly, fortnightly and monthly-basis-respectively to-maintain efficiency, effectiveness, transparency, accountability and timely transfer. The Nikshay-PFMS-interface ensured quality and delivery to the right-beneficiary.

**Results/Impact:** NPY (66%-payment) amplified NTP-performance. 53,608 of 83,000 (65%) target-TB-patients-notified, 592 of 669 (88.4%) diagnosed-DRTB-patients-treated, 52,046 of 53,283 (98%) TB-patients-tested-for-HIV, 41,087 of 53,283 (77%) eligible TB-patients-tested-for-UDST, 156,805 CBNAAT-tests-done, 11,344 of 13,214 (86%) children ≤6 years-of-age-administered-chemoprophylaxis, 47,876 of 53,283 (90%) tested-for-diabetes, and 42,776 of 53,283 (80%) known-tobacco-status with All-India-State-TB-Score of Odisha-state improved-from 27th to 15th rank during-2019.

A patient-and-provider-feedback suggested-that the-NPY-benefits offset-the-costs-of-treatment, motivated-patients to-see-treatment-earlier, improved-adherence-to-treatment and nutritional-status, and reduced-stress while around-40%-cured-patients-(TB-Champions) and their-family-members advocated-benefits-of-DBT within-their-communities/peers.

TB Notified Caes	Bank accounts opened/ available	Bank details validated by PFMS	Percentage Bank details validated by PFMS	Payable amount	Paid amount	Percentage of paid amount	TB notification rate	Success/ completion Rate
53608	48616	45960	95%	144011000	95569000	66%	65%	87.8%

[Table1. Status of Nikshay Poshan Yojana (NPY) Payments to TB Patients thru Direct Benefit Transfer (DBT) during 2019]

**Conclusions:** While free-treatment is critically-important, support-of-DBT can-make-enormous-difference to lives-and-livelihoods of-the-poor-patients. DBT-improved TB-notification-substantially while many-TB-patients migrated-from insecure-paid-treatment to-DOTS during-the-period to-avail the dual-benefits of-free-treatment and the-NPY-support.

While it is important to invest in new-diagnostic and treatment-technologies, ensuring financial-support-to-poor-TB-patients during-treatment thru-DBT will substantially-improve the-efficacy of TB-control and help-address some-of-the numerous-health-system and patient-side-barriers to-deliver-service. It is essential that stronger-political and administrative-commitment is ensured for their care and cure.

## EP10 Overcoming barriers in the contact cascade of care

### EP10-187-21 A missed opportunity: active contact investigation of diagnosed TB patients in Nigeria

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**Background and challenges to implementation:** People who have been in close contact with bacteriologically confirmed pulmonary TB patients constitute a high-risk group for developing TB disease. Contact investigation of bacteriologically confirmed index TB contributes to the early detection of TB cases and results in identifying additional TB patients.

**Intervention or response:** Through USAID funded Challenge TB project (CTB), active screening of TB patients' house hold contacts for symptomatic adults, children and PLHIVs was conducted cross 14 states from July 2016 to June 2019. Health Care Workers (HCWs), community volunteers and LGA TB and Leprosy Supervisors (LGATBLS) were engaged and trained on symptomatic screening, safe sputum specimen collection, specimen packaging, and transportation to a diagnostic facility and retrieval of test results.

**Results/Impact:** Households of 47,638 index TB patients were visited during the reporting period. In total 190,334 (~4.1 per household) household contacts screened, from whom 49,498 (25%) presumptive TB cases completed a TB evaluation, out of whom 5,445 (2.9% of all contacts) were diagnosed with TB and started treatment and a total of 5,216 children <5 years started preventive TB treatment. Household contact investigations contributed 6 % of total 94,432 TB cases notified during the period.

**Conclusions:** Active house hold contact investigation of index TB patients demonstrates a great opportunity to increase diverse pool of human resources and capacity at community levels to diagnosis and notify additional TB cases. From the success of CTB project, the current Global Fund TB grant application in Nigeria has scaled up active contact investigation as a key strategy to find and treat all missing TB patients.

**EP10-188-21 Risk of developing active MDR-TB among contacts in Taiwan, 2016-2018**

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**Background:** Contacts have been identified as an at-risk group of active tuberculosis(TB) disease. However, there remains a large gap to assess individual risk of developing active MDR-TB disease among contacts who have been exposed to a contagious MDR-TB patient.

**Design/Methods:** We conducted a cohort observational study among contacts who had been exposed to smear positive pulmonary MDR-TB index patients in the TB registry from January, 2016 to December, 2018. Baseline chest X-ray and interferon gamma release assay (IGRA) testing were provided for contacts, and those with positive or unknown IGRA results would be followed with regular Chest X-ray every 6 month for two years. The demographic information of contacts and the clinical characteristics of the index MDR-TB patients were obtained from TB registry. We followed the cohort of contacts until October 13, 2019 to calculate the incidence of MDRTB and evaluate the hazard ratio(HR) and confidence interval(CI) of developing active MDR-TB disease.

	n	Active MDR-TB diseases			Univariate		Multivariate	
		person-year	Incidence (per 100,000)	95% CI	HR (95% CI)	aHR (95% CI)		
<b>Gender of contacts</b>								
female	4	3544.2	112.9	(115.9, 272.2)	Ref.	Ref.	Ref.	Ref.
male	8	2566.6	111.8	(144.8, 502.0)	2.67	(0.80, 8.89)	2.29	(0.66, 7.96)
<b>Age group of contacts</b>								
0-24	4	1406.0	284.3	(90.4, 686.2)	Ref.	Ref.	Ref.	Ref.
25-44	2	2552.0	78.4	(11.1, 258.3)	0.36	(0.06, 1.83)	0.74	(0.12, 4.39)
45-64	3	1562.0	109.8	(117.2, 508.8)	1.19	(0.32, 4.48)	2.94	(0.65, 13.23)
>=65	1	568.7	189.9	(85.5, 437.8)	0.59	(0.07, 5.27)	0.81	(0.08, 8.48)
<b>IGRA results</b>								
positive	3	851.4	822.1	(359.6, 1,628.0)	8.81	(2.80, 27.78)	5.19	(1.53, 17.53)
negative/unknown	5	5258.8	95.1	(34.8, 235.7)	Ref.	Ref.	Ref.	Ref.
<b>Category of exposure</b>								
non-household contact	1	4530.1	66.2	(16.8, 180.2)	Ref.	Ref.	Ref.	Ref.
household contact	8	1580.1	569.6	(277.8, 1,045.0)	8.82	(2.39, 32.61)	25.36	(4.76, 135.05)
<b>Age group of index patient</b>								
0-24	4	805.7	462.1	(149.8, 1,115.0)	9.82	(1.09, 88.21)	111.56	(8.46, 1,471.36)
25-44	3	1291.8	231.9	(59.6, 611.3)	5.52	(0.57, 53.29)	5.67	(0.55, 58.36)
45-64	4	1832.3	262.8	(83.4, 633.4)	5.74	(0.64, 51.61)	6.07	(0.66, 56.07)
>=65	1	1627.5	42.3	(2.1, 203.2)	Ref.	Ref.	Ref.	Ref.
<b>Cavitary lesions on Chest X-ray of index patient</b>								
no	4	4426.1	90.4	(28.7, 238.0)	1	1	1	1
yes	8	1684.1	475.0	(203.6, 902.1)	5.07	(1.53, 16.84)	2.87	(0.79, 10.37)

[Table 1.]

**Results:** After excluding 57 contacts without complete information, a total of 2959 contacts from 168 index MDR-TB patients were enrolled. We found that 13.3% of contacts were IGRA positive. The overall incidence of MDR-TB was 196.4 per 100,000 person-year. The incidence of MDR-TB among contacts with positive IGRA was significantly higher than those with negative or unknown IGRA status (822.1 vs. 95.1 per 100,000 person-year, p<0.001).

After adjusting the contacts' age, sex, household contact or not, and the characteristics of their index case (age, cavitary lesions on chest X-ray), contacts with positive IGRA (adjusted HR(aHR): 5.19, 95% CI: 1.53-17.53) and household contacts (aHR: 25.36, 95% CI: 4.76, 135.05) were more likely to develop active MDR-TB (Table 1).

**Conclusions:** MDR-TB contacts with positive IGRA result and household exposure should be prioritized for follow-up and further intervention to detect or reduce the risk of developing active MDR-TB disease.

**EP10-189-21 Utility of interferon gamma/tumor necrosis factor alpha FluoroSpot assay in differentiation between active tuberculosis and latent tuberculosis infection: a pilot study**

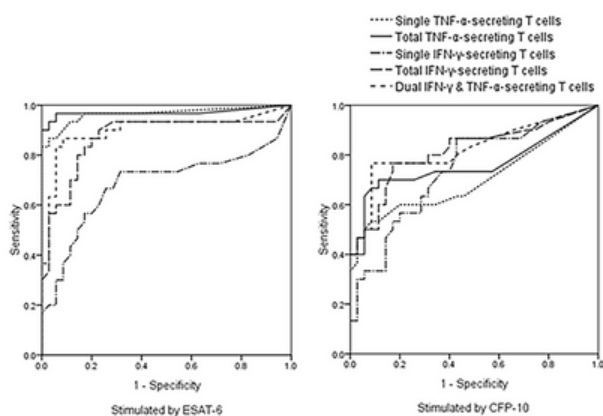
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**Background:** We aim to demonstrate the diagnostic accuracy of the IFN- $\gamma$ /TNF- $\alpha$  FluoroSpot assay of differentiating active tuberculosis from latent tuberculosis infection, as the differential diagnosis remains a challenge in clinical practice.

**Design/Methods:** In this case-control study, we performed IFN- $\gamma$ / TNF- $\alpha$  FluoroSpot assays in 30 definite cases of active TB, 35 health-care workers with latent TB infection, and 36 healthy health-care workers as controls from hospitals in Beijing, China. We obtained peripheral blood from the participants and stimulated PBMCs with MTB specific antigens(ESAT-6, CFP-10, or combined the two peptides). The IFN- $\gamma$ / TNF- $\alpha$  FluoroSpot assay visualized IFN- $\gamma$  and TNF- $\alpha$  secretion after stimulation, enabling accurate counting the frequencies of ESAT-6 and CFP-10 antigen-specific spot forming cells (SFCs). We defined the optimal cutoffs of the frequencies according to ROC curves and investigated the diagnostic accuracy of the assay.

**Results:** After ESAT-6 and CFP-10 peptides combined stimulation, the median frequencies of single IFN- $\gamma$ -, total IFN- $\gamma$ -, single TNF- $\alpha$ -, total TNF- $\alpha$ -, dual IFN- $\gamma$ /TNF- $\alpha$ -secreting T cells in active TB patients were all significantly higher than those in LTBI and control groups (P<0.05).

After ESAT-6 peptides stimulation, with cut off value of total TNF- $\alpha$ -secreting T cells frequencies at 21 iSFCs/250,000 PBMCs, the sensitivity, specificity, PLR, NLR, PPV, NPV of IFN- $\gamma$ /TNF- $\alpha$  FluoroSpot assay were 96.7%, 94.3%, 16.92, 0.04, 93.6% and 97.1%, respectively. We also found that ESAT-6 peptides stimulation presented better accuracy than CFP-10 peptides stimulation, and combined stimulation with ESAT-6 and CFP-10 peptides did not improve the differential diagnostic accuracy.



[Figure. ROC of distinct T cell subtypes in differentiating active TB and latent TB infection under combined stimulation of ESAT-6 and CFP-10]

**Conclusions:** IFN- $\gamma$ /TNF- $\alpha$  FluoroSpot assay may be useful in differentiating active TB from latent TB infection. When performing the assay, single stimulation by ESAT-6 peptides then interpreting the results at optimal cutoff reached best differential diagnostic performance, yet combined stimulation by adding CFP-10 did not improve the accuracy.

### EP10-190-21 Results of management latent tuberculosis infection 2017-2018 period in Quang Nam province, Viet Nam

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**Background:** Since 2017, the National Tuberculosis Program (NTP) wanted to strengthen that project and expand the scope of tuberculosis (TB) preventive treatment for all household contacts (HHC). The new project was piloted in Quang Nam, funded by McGill University and Woolcock Institute of Medical Research, Australia.

**Design/Methods:** The study was conducted in 5 districts of Quang Nam. The interventions was determined based on a previous survey in the community included TB patients, their relatives and health workers. Contents of intervention included: Refresh training to health workers on procedures of TB/latent TB infection (LTBI) screening; provide tuberculin and consumables to perform TST testing; travel expenses support for

contacts during the screening process. Inservice training was integrated to the routine supervision of the NTP. Number of HHC identified and started for latent TB treatment per a hundred index were used to assess the effectiveness of before and after interventions. Index patient is a pulmonary TB patient with bacteriology confirmation.

The intervention period lasted 9 months so relevant data of a cohort patient of 9 months before intervention were also collected for reference. Treatment of LTBI was not indicated for people over 50 years old.

**Results:** During intervention period, there were 259 patients registered for TB treatment, which identified 685 HHC (264 HHC/100 index), including 53 children under 5 years of age (20.5 HHC/100 Index), compared to 10.3 and 5.0/100 index respectively in before intervention. Through screening, 4 cases of pulmonary tuberculosis have been detected of which 1 case is children <5 years old. LTBI treatment were indicated to 165 (76 HHC/100 Index) including 32 children <5 years old (12.4 HHC/ Index), while no HHC had been treated of LTBI before the intervention.

**Conclusions:** Interventions have been shown to be effective in increasing the ability to identify, screen TB and treat LTBI among HHC to TB patients.

### EP10-192-21 Effectiveness of contact tracing intervention for improving TB case detection in Nigeria

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**Background and challenges to implementation:** People exposed at home to tuberculosis (TB) face high risks of the disease. Systematic investigation of contacts of TB patients is a key part of TB prevention and care strategy. The USAID funded Challenge TB project implemented an active contact investigation in Nigeria. The strategy aims at stopping TB transmission and contribute to increasing TB case finding.

**Intervention or response:** This is an active contact investigation intervention implemented across 14 states in Nigeria. The key interventions are mapping of index patients, development of SOPs for screening and contact education, capacity building for health care workers (HCWs) and community health workers (CHWs), home visit, specimen collection and transportation to diagnostic facilities for testing, linkage for TB treatment, monthly monitoring and quality improvement meeting. We analyzed TB yield and contribution to case finding in 184 areas that implemented the intervention.



**Results/Impact:** From September 2016 to June 2019, 180,480 household contacts of index TB patients were screened for TB, of whom 5,182 (3%) were found to have active TB and 5,016 initiated treatment. In addition, 4,688 under-5 children commenced isoniazid preventive therapy (IPT). TB prevalence among household contacts was therefore 2,871 / 100,000, which is 5.4 times the national prevalence in the bacteriologically confirmed adult population. CI contributed 7% (5,182/73,696) of all TB cases notified to the NTP in the period.

**Conclusions:** Active contact investigation is effective in identifying TB cases and initiating treatment to reduce transmission. It also contributes significantly to case finding. Training of HCWs and CHWs, and the use of SOPs helped to standardize TB information disseminated and empower the community with the right TB knowledge.

### EP10-193-21 Dilemma in contact investigation: to expand or not

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**Background and challenges to implementation:** Contact investigation is a key part of the TB policy in the Netherlands aiming to early detection and treatment and to prevent transmission. Risk assessment forms a basic approach to the organization of contact investigation.

**Intervention or response:** In October 2018, a Dutch student with a prolonged period of coughing was diagnosed with smear-positive pulmonary tuberculosis. Risk assessment was done by the Public Health nurse according to the stone in the pond principle and contact investigation was started. Eligible contacts were investigated in accordance with the national guidelines by tuberculin skin test (TST), interferon gamma assay (IGRA) and chest radiography (CXR).

**Results/Impact:** 65 close contacts were investigated soon after diagnosis. Latent tuberculosis infection (LTBI) was diagnosed by 24 persons, 4 persons were diagnosed with pulmonary tuberculosis (PTB).

38 persons of 143 second ring contacts were diagnosed with LTBI and 2 persons had PTB.

Among 253 people examined as third ring contacts 8 had LTBI, among them was the owner of a ski lodge where patient spent her holiday.

Ring		Number of contacts	LTBI	TB
1st	Household contacts; close friends; colleagues and classmates	65	24 (67%)	4 (6%)
2nd	Schoolmates, teachers, friends, teammates of sports club	143	38 (27%)	2 (1%)
3rd	Owners ski lodge and schoolmates, teammates, colleagues who had superficial or sporadic contacts with the index	253	8 (4%)	0
Total		461	71 (15%)	6 (1%)

[Table.]

The index patient had a unique WGS typing. The National Institute for Public Health and the Environment (RIVM) has been requested to investigate WGS connection with a patient found in March 2016, due to a documented epi link: in 2015-2016 both patients visited the same cafe. WGS differed in 20 snips, so no clustering according to Dutch guidelines. There are no patients records with the same WGS up to medio 2020.

**Conclusions:** Although high numbers of persons with LTBI found in the third ring could lead to further expansion of contact tracing, contact investigation was not expanded due to a declining trend of LTBI found from the first to the third ring and given that all contacts as described in the risk assessment were identified and investigated.

### EP10-194-21 Piloting shortened regimen for the treatment of latent TB infection in two provinces of Viet Nam

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**Background and challenges to implementation:** Treatment of latent TB infection (LTBI) is critical to achieve End TB targets. Integrating LTBI interventions into active TB case finding (ACF) can increase the number of people treated for LTBI.

**Intervention or response:** In 2019, we conducted TB and LTBI screening campaigns in three provinces of Viet Nam. We used tuberculin skin test (TST) and interferon-gamma release assay (IGRA) to assess LTBI status in contacts, healthcare workers, secondary school students (age 10-14) and other vulnerable groups. We used chest x-ray and symptom screen to rule out active TB and pro-

vided 6H regimen to children  $\leq 10$  years per the provincial TB program. We piloted the 3RH regimen in eligible participants over 10 years. Eligibility criteria included hepatic enzyme levels  $< 80$  and a negative hepatitis B/C screen. Community health workers and TB officers supported treatment monitoring.

**Results/Impact:** We tested 3,476 people for LTBI. The positivity rate was 27.6% (1,060/3,476). Of these, 92.2% (3,712/4,028) were eligible for LTBI treatment and 55.2% (2,050/3,712) were enrolled. A total of 762 (71.9%) persons were deemed eligible for LTBI treatment. Of these, we enrolled 86.7% (661/762) person among whom we administered 3HR in 96.5% (638/661) of cases, while 3.5% (23/661) were provided 6H. About 74.9% (495/661) completed treatment. This included a completion rate of 75.0% (492/656) among persons enrolled on 3HR and 60.0% (3/5) among children treated with 6H.

**Conclusions:** We found and treated a large number of persons with LTBI using shortened LTBI regimen. Use these shortened regimen may have helped to increase participation and achieve a promising completion rate. The results of this study subsequently contributed to the revision of national LTBI guidelines to include 3HR as an approved treatment regimen. Scale-up of LTBI should consider this regimen a strong alternative to the traditional 9H regimen.

### EP10-195-21 Prevalence of latent tuberculosis infection and predictive factors among working-age population in urban and rural area of Northern Guangdong, China: a cross-sectional study

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**Background and challenges to implementation:** China has one of the highest burdens of latent tuberculosis infection (LTBI), especially in high-risk populations such as household contacts of TB cases, adolescents, health care workers, people living with HIV and detainees. But little is known about the burden of LTBI in working-age population.

**Intervention or response:** Using a community-based survey with random sampling, we examined the burden of LTBI among working-age population (aged 15 to 64 years) with Interferon- $\gamma$  Release Assay (IGRAs). Multi-level logistic models based on household-level data and individual-level data were used to identify factors associated with LTBI.

**Results/Impact:** This analysis included 1022 households, totally 1614 participants from urban and rural area of Northern Guangdong. The overall prevalence of LTBI was 23.6% (350/1614, 95% CI: 21.8%, 25.5%). LTBI was associated with individual-level characteristics, including age (aOR=1.030 for every year increased in age, 95% CI=1.015-1.044), male gender (aOR=1.782, 95% CI=1.364-2.329), lower education level (primary/below aOR=1.966, 95% CI=1.024-3.776; middle/high school aOR=1.996, 95% CI=1.061-3.756), urban residence (aOR=1.444, 95% CI=1.114-1.870), smoking (aOR= 2.882, 95% CI=1.102-7.538), and history of dust exposure at work (aOR= 1.904, 95% CI=1.046-3.466).

**Conclusions:** The prevalence of LTBI in working-age population increased with age. The annual risk of infection with *M. tuberculosis* is high in men and urban residents. Population with history of dust exposure at work and low education level should be aware of TB infection, especially smokers. More definitive, mechanistic studies are needed to cement the effect of smoking and dust exposure on LTBI pathogenesis and to utilize this knowledge in empowering public health policies.

### EP10-196-21 Impact of civil society advocacy on the introduction of TB LAM testing in PEPFAR-eligible countries

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**Background:** Uptake of lipoarabinomannan (LAM) testing in high tuberculosis (TB) and HIV burden countries has been limited despite demonstrated mortality benefit among people with advanced HIV,<sup>1</sup> and availability of donor funding.<sup>2,3</sup> During FY2019 U.S. President's Emergency Plan for AIDS Relief (PEPFAR) Country Operational Plans (COPs) development, civil society advocated for the inclusion of language and targets for LAM testing in COPs during national and regional consultations.

<sup>1</sup>Peter JG, Ziejenah LS, Chanda D, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group,



multicountry, open-label, randomised controlled trial. *Lancet*. 2016 Mar 19; 387(10024):1187–97. [https://doi.org/10.1016/S0140-6736\(15\)01092-2](https://doi.org/10.1016/S0140-6736(15)01092-2).

<sup>2</sup>U.S. President's Emergency Plan for AIDS Relief. PEPFAR 2018 Country Operational Plan Guidance for Standard Process Countries. U.S. Department of State: 2018. [https://na.usembassy.gov/wp-content/uploads/sites/132/PEPFAR-COP18-Guidance\\_FINAL-1.pdf](https://na.usembassy.gov/wp-content/uploads/sites/132/PEPFAR-COP18-Guidance_FINAL-1.pdf).

<sup>3</sup>U.S. President's Emergency Plan for AIDS Relief. PEPFAR 2019 Country Operational Plan Guidance for all PEPFAR Countries. U.S. Department of State: 2019. <https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf>.

**Design/Methods:** We evaluated available FY2018 and FY2019 PEPFAR COPs (N=25/64) to determine the impact of advocacy on LAM uptake. We searched final COPs for: “LAM”; “lipoarabinomannan”; “TB LAM”; “Determine LAM ag”; “LF-LAM”; and “lateral flow”, and analyzed relevant language to evaluate changes in LAM uptake in PEPFAR-supported programs between FY2018 and FY2019.

**Results:** Between FY2018 and FY2019 the number of PEPFAR-eligible countries including LAM testing in COPs doubled from 6 to 12 (Table 1). Countries that included LAM testing for the second consecutive year generally included more specific implementation plans.

**Conclusions:** Uptake of LAM testing within PEPFAR-supported programs remains low but improved following civil society advocacy. Our analysis underscores the added benefit of civil society involvement in PEPFAR COPs development, especially as the evidence base and policies for routine LAM testing expand, and as next-generation tests with improved sensitivity are poised for market entry.

Country	Population for use described in PEPFAR COP		Country	Population for use described in PEPFAR COP	
	FY2018	FY2019		FY2018	FY2019
Côte d'Ivoire	PLHIV with advanced disease	PLHIV with advanced disease	Namibia		PLHIV with advanced disease
Democratic Republic of the Congo	PLHIV with low CD4 counts or those who are seriously ill	PLHIV with low CD4 counts or those who are seriously ill	South Africa		Hospitalized PLHIV with advanced disease
Eswatini	PLHIV who present to care late	PLHIV with CD4 counts <100 cells/mm <sup>3</sup> or seriously ill	Tanzania		PLHIV with advanced disease and CD4 counts < 200 cells/mm <sup>3</sup> , or seriously ill
Kenya	Hospitalized PLHIV	Severely sick hospitalized PLHIV	Uganda		PLHIV with advanced disease
Lesotho		PLHIV with CD4 counts <200 cells/mm <sup>3</sup>	Ukraine		PLHIV with advanced disease
Malawi	PLHIV	PLHIV with advanced disease, CD4 counts < 200 cells/mm <sup>3</sup> , or seriously ill	Zambia	Not specified	Not specified

**PEPFAR-eligible countries (N=64):** Angola, Antigua and Barbuda, Bahamas, Barbados, Belize, Botswana, Brazil, Burundi, Cambodia, Cameroon, China, Costa Rica, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Dominica, Dominican Republic, El Salvador, Eswatini, Ethiopia, Ghana, Grenada, Guatemala, Guyana, Haiti, Honduras, India, Indonesia, Jamaica, Kazakhstan, Kenya, Kyrgyzstan, Laos, Lesotho, Malawi, Mali, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Nigeria, Panama, Papua New Guinea, Rwanda, Senegal, Sierra Leone, South Africa, South Sudan, St. Kitts and Nevis, St. Lucia, St. Vincent, Suriname, Tajikistan, Thailand, Trinidad and Tobago, Turkmenistan, Uganda, Ukraine, Uzbekistan, Tanzania, Vietnam, Zambia, Zimbabwe

**Countries whose FY2018 and FY2019 COPs were available (N=25):** Angola, Botswana, Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Dominican Republic, Eswatini, Ethiopia, Haiti, Kenya\*, Lesotho, Malawi, Mozambique, Namibia, Nigeria, Rwanda, South Africa, South Sudan, Tanzania, Uganda, Ukraine, Vietnam, Zambia, Zimbabwe

\*For FY2019, reviewed unpublished draft COP

**Countries with high burdens of TB and HIV (N=30):** Angola, Botswana, Brazil, Cameroon, Central African Republic, Chad, China, Congo, Democratic Republic of the Congo, Eswatini, Ethiopia, Ghana, Guinea-Bissau, India, Indonesia, Kenya, Lesotho, Liberia, Malawi, Mozambique, Myanmar, Namibia, Nigeria, Papua New Guinea, South Africa, Tanzania, Thailand, Uganda, Zambia, Zimbabwe

**FY2018 PEPFAR Country Operational Plans that include language on TB LAM testing (N=6):** Côte d'Ivoire, Democratic Republic of the Congo, Eswatini, Kenya, Malawi, Zambia

**FY2019 PEPFAR Country Operational Plans that include language on TB LAM testing (N=12):** Côte d'Ivoire, Democratic Republic of the Congo, Eswatini, Kenya, Lesotho, Malawi, Namibia, South Africa, Tanzania, Uganda, Ukraine, Zambia

[Table 1. Analysis of TB LAM Inclusion in FY2018 and FY2019 PEPFAR COPs]

## ABSTRACT PRESENTATIONS THURSDAY 22 OCTOBER 2020

### ORAL ABSTRACT SESSION (OA)

#### OA-10 Partnerships for integrating services

##### OA-10-556-22 Engaging private health care providers to intensify TB case detection

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**Background and challenges to implementation:** Anecdotal evidence shows that private health care providers play a major role in TB referrals, diagnosis and treatment, especially in urban areas. The private sector is often the first point of contact for persons presumed to have TB. However, persons with TB are often poorly managed in the private sector. This can result in the delay of treatment, continued transmission, and increased drug resistance.

A WHO study conducted in 2006, suggests that 30-35% of the total cases of TB are from the private sector. But recently reported Nepal National Tuberculosis Program (NTP) data, shows only 17% contribution from the private sector. Sahayog Samittee Nepal (SS Nepal) implemented a TB REACH project that aims to address the 13-18% gap in TB cases notifications from the private sector in an urban area.

**Intervention or response:** We mapped 124 and prioritized 63 private health care providers (PHCPs) in two urban districts (Parsa and Dhanusha) of province 2 in Nepal. A cough screening desk (CSD) was implemented, in each prioritized PHCPs. Staff of the PHCPs clinic were enlisted to screen all the persons visiting the CSDs. We trained the CSD workers on screening and provided doctors an orientation on the NTP policy. For logistical support, we coordinated with the National Tuberculosis center, provincial health directorate, district health offices and local government. To assess impact,

we compared notification data of bacteriologically confirmed and clinically diagnosed cases from baseline to the implementation period in our intervention area.

**Results/Impact:** From November 2018 to January 2020, 203,332 persons were screened for TB at CSDs of which 11266 were presumptive for TB. 8077 presumptives were tested of which 682 were diagnosed with TB.

Baseline		Implementation period		Additionality		% change from baseline	
Bacteriological Positive cases	All forms cases	Bacteriological Positive cases	All forms cases	Bacteriological Positive cases	All forms cases	Bacteriological Positive cases	All forms cases
1262	2422	1472	2670	210	248	17%	10%

[Figure 1.]

**Conclusions:** The result of the intervention emphasizes the importance of effectively engaging private health care providers in TB program to achieve NTP goals.

##### OA-10-557-22 Rational medicine use when presented with TB symptoms: private sector prescribing practices in two urban regions of South Africa

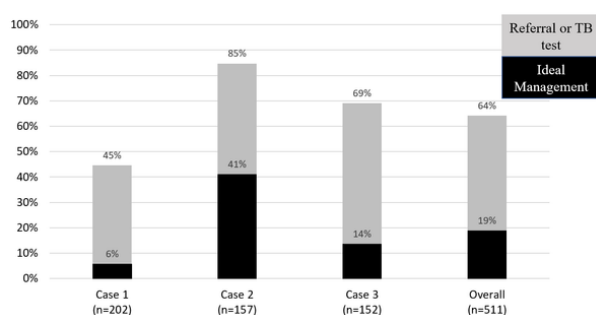
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**Background:** The WHO and South African National Drug Policy encourage rational use of medicines, ensuring patients receive the most appropriate drugs at the lowest cost. About 1/3 of South African patients with TB symptoms first seek care in the private sector, but little is known about medicine use in this setting. We describe drug prescribing practices for patients with TB symptoms among private general practitioners (GPs) in two urban areas of South Africa.

**Design/Methods:** Cash-paying patient-actors presented one of the three TB cases during unannounced visits to consenting GPs in 2018-2019: TB symptoms with HIV (case 1), microbiologically confirmed TB, without HIV (case 2), and TB symptoms with history of TB treatment and HIV (case 3). We documented visit details using standardized questionnaires. We analyzed drug-pres-

scribing (including dispensing) practices and ideal case management (referral to clinic or TB testing without prescription of antibiotic or steroid).

**Results:** Patient-actors completed 511 visits with 213 GPs. In 360/511 (71%) interactions,  $\geq 3$  medicines were prescribed (mean=3.09, SD=1.6 per interaction). Common prescriptions included antibiotics (76%, of which 9% were fluoroquinolones, and 1% anti-mycobacterials) and steroids (18%). Patient-actors were offered an injection in nearly one-third of visits (1.8% antibiotic, 0.6% vitamin, 97.6% unknown). Cotrimoxazole was prescribed in 11.4% of all visits and 13.1% of visits in which HIV status was negative or not ascertained. Patient-actors were referred to clinic or offered TB testing in 64% of visits but ideally managed in only 19% (Figure). Case 2 received fewer antibiotics (OR=0.21, 95% CI 0.14-0.33) and steroids (OR=0.35, 95% CI 0.19-0.63) than cases 1 and 3.



[Figure. Referral or TB test vs. ideal management of patient actors]

**Background and challenges to implementation:** The WHO and South African National Drug Policy encourage rational use of medicines, ensuring patients receive the most appropriate drugs at the lowest cost. About 1/3 of South African patients with TB symptoms first seek care in the private sector, but little is known about medicine use in this setting. We describe drug prescribing practices for patients with TB symptoms among private general practitioners (GPs) in two urban areas of South Africa.

**Conclusions:** While prescription of fluoroquinolones and anti-TB medications was relatively low, over-prescription (especially of antibiotics) was frequently observed amongst participating GPs. Ideal care improved when TB was microbiologically confirmed. These prescribing practices potentially carry significant implications for antimicrobial drug-resistance, TB diagnostic delay, and healthcare costs in South Africa.

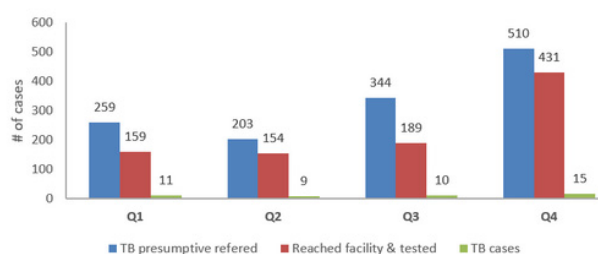
## OA-10-558-22 Engaging informal providers to screen and refer TB presumptives cases for formal TB diagnosis: use of barcode sticker system to refer TB presumptives

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**Background and challenges to implementation:** Malawi's National Tuberculosis (TB) Guidelines and TB strategic plan recommends engaging informal providers (IP) to screen all clients for TB and refer all TB presumptives to facility for TB diagnosis. However, engaging informal providers has been challenging. Past experience revealed that many clients who visited the informal providers, once referred, do not reach the health facilities for final TB diagnosis due to various factors. CHAI and the NTP developed a systematic package of actively engaging traditional healers, pharmacies and drug stores to actively screen, refer and follow up TB presumptives for formal TB diagnosis at the facility in 2 districts in Malawi.

**Intervention or response:** We developed a TB screening package including a training curriculum, IP TB presumptive register, IP referral slips and barcode sticker system. From February to December, 2019, trainings were administered to 278 informal providers. Subsequent mentorship visits and cluster review meetings were conducted to informal providers. Client data from IP TB presumptive register were compared to facility TB presumptive register. TB presumptives from IPs were identified using the barcode sticker and missing clients who did not reach the facility and needed follow up were identified if the barcode sticker was not available at the facility in the TB presumptive register.

**Results/Impact:**



[Figure 1. Number of TB presumptives cases referred, reached facility and tested TB cases identified]

From February to December a total of 1,316 TB presumptives were referred from informal providers to health facility for TB diagnosis using the barcode sticker system. A total of 933 (71%) TB presumptives reached the facility and were tested for TB. 45 (4.8%) were diagnosed with TB. Based on this initial success on referrals and yield identified, NTP and other partners are currently in a process of scaling up this model.

**Conclusions:** This intervention demonstrated the potential to increase TB notifications through actively engaging informal providers to screen, refer and follow up TB presumptives.

### OA-10-559-22 "Integrating services of tuberculosis, HIV/AIDS and malaria at the community level" lessons from community systems strengthening pilot project in Kenya

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**Background and challenges to implementation:** Various partners implement vertical community health initiatives contributing to fragmented service delivery. To assess the feasibility of integrating the services of HIV/AIDS, TB and Malaria at the community level, Amref Health Africa in Kenya through Global Fund project supported implementation of community Systems strengthening (CSS) integrated model in three sub counties in Kenya.

**Intervention or response:** The project was implemented between October 2016 and September 2019 in 3 sub counties; Lunga, Emuhaya and Rangwe. A total of 942 Community Health volunteers (CHVs) were trained on service delivery for the three diseases using the integrated CHV curriculum. The Community Health extension workers (CHEWs) offered supportive supervision to ensure quality work.

For HIV/AIDS, the CHVs conducted home-based care, referral for testing and counselling and tracing treatment interrupters. For Malaria the CHVs tested and treated uncomplicated malaria cases and referred severe cases.

For TB, the CHVs Traced contacts of bacteriologically confirmed TB patients to identify and refer presumptive TB people. They also offered health education on the three diseases.

Baseline data for 2016 and end line data for 2019 was collected and compared.

**Results/Impact:** There was improvement in the indicators reported across the three diseases. For HIV/AIDS, number of positive cases notified reduced by 23% (2361 to 1826) while number of ART interrupters traced increased by 27% (116 to 147). For TB, number of people with TB referred by CHVs increased by 99% (138 to 274), whereas number of TB people provided with Direct Observation Therapy by CHVs increased from 22 to 787. For Malaria, number of cases treated with ACT

increased by 237% (10,531 to 35,445), while referral of pregnant women to health facilities increased by 68% (3931 to 6593).

**Conclusions:** Services for the three diseases improved when offered through the integrated model. This model can be scaled-up to other regions for better health service delivery.

### OA-10-560-22 Adherence to TB screening and treatment initiation guidelines in urban Nigeria: a study of TB care quality among private clinical providers in two states

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**Background:** The WHO classifies Nigeria as high burden country for TB. Nigeria's national program to diagnose and treat TB was largely limited to the public sector; the large footprint of Nigeria's private health sector represents an untapped resource for combating the disease. The USAID-funded Sustaining Health Outcomes through the Private Sector (SHOPS) Plus program implemented a study to evaluate the extent that private clinical facilities it trained to provide TB services adhere to national standards for management of presumptive and confirmed TB.

**Design/Methods:** The study used a standardized patient (SP) survey--considered the "gold standard" for examining provider behavior--and a medical vignette survey to assess provider knowledge gaps. The sample included 398 clinical facilities in urban areas of Lagos and Kano States. Two different patient scenarios were examined -- a "textbook" case of presumptive TB and a treatment initiation case in which SPs present as referred patients with confirmed TB diagnoses.

**Results:** Although a majority (73%) of clinical providers appropriately screened the presumptive TB case, few SPs received fully-correct management (31%). Clinical providers recommended/requested sputum tests, X-rays, and HIV tests less often than with hypothetical clients in the vignette survey. In the treatment initiation case only 18% of providers demonstrated fully-correct SP management. Bottleneck analysis revealed: 1) the most common deviation from correct management was a failure to initiate sputum collection for testing and, 2) a failure to conduct sufficiently thorough treatment initiation counseling for confirmed TB patients.

**Conclusions:** Results indicate an adaptive management opportunity for SHOPS Plus. The program is identifying ways to better sensitize private clinical providers to TB management protocols by adjusting supportive supervision and developing provider-centric job aids. A planned follow-up survey before the end of the project

will assess effectiveness of such support to improve the quality of TB care provided by SHOPS Plus-affiliated providers.

		n (%)	95% CI
Scenario 1: Patient presents with a cough and fever (n=269)	Criterion 1: Asked about duration of productive cough and one more TB symptom	196 (72.9%)	69.5%, 76%
	Criterion 2: Provider recommended/attempted to take a sputum sample, recommended chest x-ray, or referred MC for diagnosis elsewhere	150 (55.8%)	51.9%, 59.5%
	Criterion 3: No prescription of unnecessary antibiotics, anti-TB drugs, or steroids	163 (60.6%)	56.8%, 64.3%
	Successful patient management (Met all 3 criteria)	84 (31.2%)	27.7%, 34.9%
Scenario 2: Patient presents with a positive GeneXpert test result (n=255)	Criterion 1: Confirmation of diagnosis	185 (72.6%)	68.2%, 76.7%
	Criterion 2: Explanation of disease and treatment	114 (44.8%)	40.2%, 49.6%
	Criterion 3: Requests patient to identify a treatment supporter	95 (37.2%)	32.7%, 41.9%
	Criterion 4: No prescription of non-TB antibiotics, steroids	213 (83.4%)	79.5%, 86.7%
	Criterion 5: Prescription/provision of TB drugs for treatment OR requests patient to come back with the treatment supporter to initiate treatment	179 (70.0%)	65.7%, 73.9%
	Successful patient management (Met all 5 criteria)	47 (18.4%)	15%, 22.4%

[Table 1. Summary standardized patient survey results]

### OA-10-561-22 Provider initiated Active TB Case finding in high volume health care facilities: preliminary results from an ongoing project in Nigeria

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**Background and challenges to implementation:** Nigeria ranks 6th among the high burden countries for TB with an estimated incidence of 219/100,000 and accounts for 12% of the gap of unidentified TB cases globally. This gap between notified and estimated cases is largely due to underreporting and under diagnosis. To address these two factors, KNCV Nigeria USAID-funded Active TB case finding project, introduced a provider-initiated TB case finding in health facilities.

**Intervention or response:** This intervention commenced in February 2020 and is currently on going in 9 states in Nigeria. 61 High volume secondary and tertiary public facilities were selected following a baseline assessment. Designated Screening officers and facility staff were trained on the use of symptom checklist to screen all clinic attendees for TB, identify presumptive TB, linkage for diagnostic evaluation and treatment for confirmed TB cases. Data was reported real time using COM-MCARE mobile application. Monthly meetings were held to review implementation.

**Results/Impact:** Within 2 months of implementation, preliminary results show an increase in awareness about TB in the facilities. Staff ensure clients are screened either by referral to the screening officers or by themselves when screening officers are not available. A total of

281,391 hospital attendees were screened, 14,558 identified presumptive TB had diagnostic evaluation, 1547 TB cases were diagnosed representing a 40% increase from baseline which was 929 for the 2 months preceding intervention. One thousand one hundred and seventy-seven of the diagnosed TB patients (76%) were placed on treatment. Overall yield from the screening was 0.6%; Number Needed to screen was 182; Number Needed to test was 9.

**Conclusions:** Provider initiated screening of clinic attendees has the potential to increase TB case finding. This kind of intervention can be replicated in similar settings to further narrow the gap in TB case detection in Nigeria.

### OA-10-562-22 Significant boost needed to ensure sustainable procurement by governments of WHO-recommended TB medicines in high burden TB countries while shifting from donor-supported to domestically-funded procurement

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**Background and challenges to implementation:** Increasingly, donors are requesting countries to dedicate government funds to pharmaceutical purchase. Countries need to rely on national procurement mechanisms: local registration is compulsory for manufacturers to bid in national tenders and importation often conditioned by inscription on the national Essential Medicine Lists (nEMLs).

**Intervention or response:** The #StepUpforTB 2020 study assessed policy-adoption of international best practices and innovations on TB diagnosis, prevention, treatment and drug regulation in 43 high TB burden countries by the end of December 2019. National TB Programme managers or assigned focal points were interviewed with a semi-structured questionnaire. A desk review of national policy documents was part of the data review. The overall response rate was 84%.

**Results/Impact:** For Drug-Sensitive TB (DS-TB) in adults, less than 16/36 countries registered at least one World Health Organisation (WHO)-recommended fixed-dose combination (FDC), being WHO-prequalified or registered by a Stringent Regulatory Authority. Outcomes are similar for medicines for Drug-Resistant TB (DR-TB). For paediatric TB formulations, only 9/36 countries registered at least one WHO-prequalified FDCs for DS-TB and less than 10% did for DR-TB dispersible formulations. 22/36 countries were enrolled in the WHO Collaborative Registration Procedure (CRP),

but only 11/36 used this mechanism to register TB medicines. 12/36 countries had bedaquiline in their nEML, but only 8 countries listed all new and repurposed TB medicines. In 12/36 countries, regulations imposed TB drug selection criteria, winning bidding companies and final pricing were made publicly available in national tenders.

**Conclusions:** MSF calls for urgent technical assistance from donors and WHO to enhance mutual recognition between regulatory agencies, ensure transparency in national tenders and promote updates of nEMLs. The use of the WHO CRP and other regulatory mechanisms incentivising mutual recognition should be maximised by countries and manufacturers. These are prerequisites to ensure sustainable access to quality-assured TB medicines when countries shift to domestic financing for medical procurement.

## OA-11 New solutions to old TB challenges

### OA-11-563-22 Comparison of three bacteriological methods of Mycobacterium tuberculosis in cerebrospinal fluid

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**Background:** Tuberculosis meningitis (TBM) is common extrapulmonary tuberculosis that causes high mortality and disability. Detection of Mycobacterium tuberculosis (MTB) in cerebrospinal fluid (CSF) is the gold standard for diagnosis of TBM. We aim to evaluate the value of three bacteriological methods in diagnosis of TBM.

**Design/Methods:** We enrolled 112 patients with suspected meningitis from September 2017 to June 2019 in Beijing Chest Hospital, 263 Hospital of the PLA (People's Liberation Army) and Beijing Chaoyang Hospital. TBM was diagnosed according to the definition which was published in 2010. Definite TBM, probable TBM and possible TBM were belonged to the TBM-group. Patients with other central nervous system diseases were classified as non-TBM group. The CSF specimens of the patients were collected for MTB cell-free DNA (cf-TB) test, MTB culture and Xpert MTB/RIF test. SPSS21.0 was used for statistical analysis.

**Results:** A total of 90 patients were included in this study. The sensitivity of cf-TB test, MTB culture and Xpert MTB/RIF test was 50.0% (95% CI 37.6%~62.4%), 7.6% (95% CI 2.8%~17.5%) and 15.4% (95% CI 8.5%~25.7%), respectively. The specificity were all 100% (95% CI 82.8%~100%). The sensitivity of cf-TB

test was significantly higher than that of MTB culture and Xpert MTB/RIF test, the differences were all statistically significant ( $P=0.000$ ;  $P=0.000$ ). The positive rate of cf-TB test in the definite TBM, probable TBM, and possible TBM groups was 93.8% (15/16), 45.5% (15/33), and 17.6% (3/17), respectively. The positive rate of cf-TB test in definite TBM group was significantly higher than the probable ( $P=0.001$ ) and possible group ( $P=0.000$ ). There was no statistical difference between the probable and possible TBM groups ( $P=0.052$ ).

	TBM (n=66)	Non-TBM (n=24)	P
Year (yr)	37.3±18.5	41.4±16.8	0.341
Male patients (%)	39 (59.1)	16 (66.7)	0.514
Time of onset to treatment (days)	30 (20,90)	7 (5,16)	0.000
Abnormal on brain MRI (%)	49 (74.2)	5 (20.8)	0.000
Fever (%)	56 (84.8)	4 (16.7)	0.000
Disturbance of consciousness (%)	20 (30.3)	2(8.3)	0.032
CSF WBC ( $\times 10^3/\mu\text{l}$ )	97 (19.3,226)	7.0 (3.3,113.5)	0.001
CSF glucose (mmol/L)	2.3±0.8	3.4±1.0	0.000
CSF protein (g/L)	1.3±1.1	0.3±0.4	0.000

**Conclusions:** The sensitivity of cf-TB test in CSF was significantly higher than MTB culture and Xpert MTB/RIF. Further research should be done to evaluate the value of these tests in diagnosis of TBM.

### OA-11-564-22 Non-invasive respiratory aerosol sampling using masks for detection of pulmonary tuberculosis in children

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**Background:** Children with pulmonary tuberculosis (PTB) find it difficult to produce sputum necessitating invasive sample collection methods for diagnosis. Recently we demonstrated the potential of a novel and non-invasive mask based respiratory aerosol sampling method for detection of PTB in adults with productive and unproductive cough. Being a non-invasive method, this study aimed to evaluate this method for diagnosis of paediatric PTB.

**Design/Methods:** Ten children median age 11, with confirmed diagnosis for PTB from gastric lavage (GL; n=7) or sputum (n=3) were recruited before initiation of treatment at TB clinic of BJWHC. Children wore an N-95 mask attached with gelatin membrane for 10 minutes, during which they talked/recited, coughed, and took tidal breaths 20 times each to collect expelled and exhaled aerosols on the membrane. Two membrane samples were collected from each child- one in a GeneXpert reagent

for detection by GeneXpert and the other in RNAzol for detection of TB specific RNA (16s, rpoB, sigA, and fgd-1) by SYBR green quantitative PCR (qPCR).

**Results:** Nine of 10 patients had TB confirmation in the GL/sputum by GeneXpert (n=3) or GeneXpertUltra (n=7) while one patient's GL was negative by GeneXpertUltra but positive by smear microscopy. Of the 7 GL confirmed children, only one patient had a positive GeneXpert mask sample whereas 6 patients were positive by mask RNA-qPCR. In 3 sputum confirmed patients, zero samples were positive by GeneXpert while all 3 patients had positive RNA-qPCR in the mask. The number of TB genes detected by qPCR were 0/4 (n=1), 1/4 (n=1), 2/4 (n=1), 3/4 (n=3) and 4/4 (n=4).

**Conclusions:** We demonstrate here a proof of concept of respiratory aerosol sampling on masks combined with RNA-qPCR to detect TB in children. The method is non-invasive and simple with comparable results to standard methods. The study has significant implications in paediatric pulmonary TB diagnosis.

#### OA-11-565-22 Stool-based Xpert Ultra testing for childhood TB in Kampala, Uganda

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**Background:** Sputum collection for tuberculosis (TB) is challenging in children. Molecular stool testing has had utility, but is limited by the need for centrifugation. We evaluated the role of a centrifuge-free stool processing method to diagnose childhood pulmonary TB.

**Design/Methods:** We consecutively enrolled children under 15 years being assessed for pulmonary TB in Kampala, Uganda. Respiratory specimens were obtained for Xpert MTB/RIF Ultra (Ultra), smear microscopy, and liquid and solid culture.

We collected stool before treatment initiation, and used the FIND Stool Processing Kit (SPK) followed by Ultra testing (SPK-Ultra). We compared the sensitivity and specificity of SPK-Ultra to sputum Xpert Ultra and smear microscopy using confirmed and unlikely TB as the reference. We calculated any sensitivity improvement with a second SPK-Ultra, and the yield in children with unconfirmed TB.

**Results:** We enrolled 96 children, including 29 (30%) with confirmed TB. Median age was 4 years (IQR 1.95-7.6), 51% were male, 11% were HIV-positive (CD4 count median 884 cells/ul, IQR 625-1272), 59% were underweight, and 32% had diarrhea. Six (6.3%) stool Ultra tests were invalid, but were valid on repeat testing. SPK-Ultra was positive in 14 (15%) children, with sensitivity 44.8% (95% CI 26.4-64.3) and specificity 98.1% (95% CI 89.9-100). Sensitivity was similar to smear (sensitivity 37.9%, -6.8% difference, 95% CI -23.6 to +9.8, p=0.63). Among culture positive cases, sensitivity was lower than sputum Ultra (57.1% vs. 71.4%, difference -14.3%, 95% CI -34 to 5.4, p = 0.25), although not statistically significant. Sensitivity was similar by category of age (p=0.37), weight (p=0.4) and diarrhea (p=1.0). A second Ultra test was 100% concordant and did not increase yield. No children with unconfirmed TB had a positive SPK-Ultra result.

**Conclusions:** Stool SPK-Ultra detected almost half of children with confirmed TB and had similar performance to smear, and should be considered when sputum collection is not possible.

#### OA-11-566-22 Development of a treatment-decision algorithm for HIV-uninfected children with presumptive pulmonary tuberculosis

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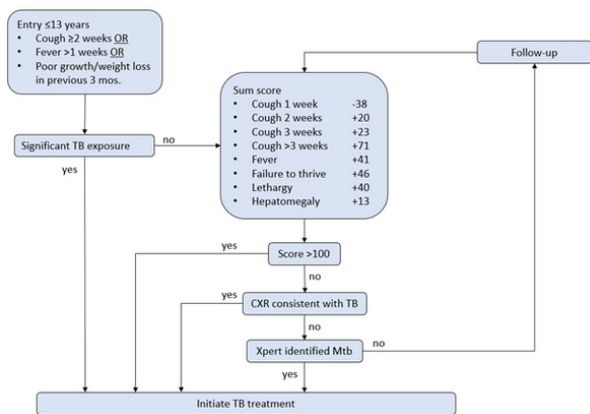
**Background:** Over 96% of childhood tuberculosis deaths occur among children not receiving antituberculosis treatment, with most cases and death occurring among young, HIV-uninfected children. Improved clinical diagnosis among young children, who commonly have paucibacillary disease, is critical to initiating more children with tuberculosis on appropriate treatment. We developed treatment-decision scores to guide anti-tuberculosis treatment decision-making among HIV-uninfected children evaluated for pulmonary tuberculosis (PTB).

**Design/Methods:** We performed analysis on data from a prospective cohort of HIV-uninfected children evaluated for suspected PTB in Cape Town, South Africa, who underwent clinical assessment, chest radiography (CXR), and sample collection for microbiology. We used logistic regression to develop tuberculosis diagnostic models with (1) clinical history and examination, CXR, and Xpert and (2) without CXR and Xpert as predic-



tors. We developed prediction scores for each model with sensitivity set at 90%. Data were analyzed retrospectively and had no impact on clinical management.

**Results:** Data were complete for 478 HIV-uninfected children (median age: 16.2 months, IQR: 9.8-30.9) for all modeled variables; 242 (50.6%) had tuberculosis, including 104 (21.8%) microbiologically-confirmed. Predictors in the final models included: cough duration, fever, failure to thrive, lethargy, significant tuberculosis exposure, hepatomegaly, CXR, and Xpert. The prediction score for model (1) had a sensitivity of 90.1% and specificity of 52.5%. CXR had a higher sensitivity than Xpert among children not meeting the model (1) threshold score to begin antituberculosis treatment after clinical history and examination. The score for model (2) had a sensitivity of 90.5% and specificity of 34.0%.



[Figure: Treatment-decision algorithm based on model (1).]

**Conclusions:** Clinical history and examination provided sufficient evidence to make antituberculosis treatment decisions. In settings where high-quality CXR and Xpert are available, CXR should be pursued first. Starting more children on antituberculosis treatment based on robust clinical algorithms will contribute substantially to reducing the global burden of tuberculosis and childhood mortality.

**OA-11-567-22 Evaluation of Mycobacterial SmartProbes: novel fluorescent probes for the detection of live mycobacteria in diagnostic samples**

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**Background:** Due to its low cost and long history of use, sputum smear microscopy is widely used to screen for suspected pulmonary TB. However, these microscopy

tests depend on stain-based methods that were developed over 100 years ago and require extensive processing and washing steps, resulting in detection levels as low as ~30%, depending on factors such as experience of the user and quality of sample. Here, we show the results of evaluation conducted at CTRI (Moscow, Russia), of the novel fluorescent trehalose-based probes (Mycobacterial SmartProbes) developed by the University of Edinburgh, UK.

**Design/Methods:** *M.tuberculosis* H37Rv culture and smear-positive sputum from TB patients were used for fluorescent Mycobacterial SmartProbes testing. Culture was washed from the liquid media using saline. The sputum (20 samples) was decontaminated with NALC-NaOH and washed with phosphate buffer. The samples were incubated with Mycobacterial SmartProbes at 37°C in the dark for 30 min, then washed from the unbound dye with saline. The smear was applied to the slide and allowed to dry in the dark. Auramine-rhodamine staining was used as a control. The staining results were detected using the “Axiostar” fluorescent microscope (Carl Zeiss, Germany).

**Results:** The microscope settings and the visualization results are shown in the table.

Mycobacterial SmartProbes	Formula	Microscope filter (excitation filter/dichroic reflector/emission filter)	Quality of incorporation of SmartProbes in mycobacterial cell wall: culture / sputum	Picture contrast (cells-background): culture / sputum
MU-198 (TreG)	C <sub>26</sub> H <sub>33</sub> N <sub>5</sub> O <sub>13</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Optimal / Optimal
MU-202 (TreR)	C <sub>42</sub> H <sub>48</sub> N <sub>2</sub> O <sub>15</sub> S	FS20 (BP 546/12 / FT 560 / BP 575-640)	Normal / Normal	Optimal / Optimal
MU-232	C <sub>21</sub> H <sub>25</sub> N <sub>2</sub> O <sub>8</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Optimal / Optimal
MU-236	C <sub>26</sub> H <sub>32</sub> N <sub>2</sub> O <sub>12</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Optimal / Optimal
MU-217	C <sub>21</sub> H <sub>17</sub> N <sub>7</sub> O <sub>13</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Low picture contrast / Low picture contrast
MU-161	C <sub>34</sub> H <sub>42</sub> BF <sub>2</sub> N <sub>5</sub> O <sub>11</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Optimal / Optimal
AB-74	C <sub>31</sub> H <sub>39</sub> N <sub>5</sub> O <sub>13</sub>	FS01 (BP 365/12 / FT 395 / LP 397)	Normal / Normal	Optimal / Optimal
MU-224	C <sub>48</sub> H <sub>57</sub> N <sub>7</sub> O <sub>17</sub> S <sub>2</sub>	FS20 (BP 546/12 / FT 560 / BP 575-640)	Low quality / Low quality	Low picture contrast / Low picture contrast
MU-234	C <sub>43</sub> H <sub>46</sub> N <sub>4</sub> O <sub>13</sub> S	FS20 (BP 546/12 / FT 560 / BP 575-640)	Normal / Normal	Optimal / Optimal

[Table.]

**Conclusions:** 7 of 9 fluorescent Mycobacterial SmartProbes have been identified which optimally stain the *M.tuberculosis* culture and mycobacterial-positive smears. The Mycobacterial SmartProbes are suitable as the basis for the creation of a new test for pulmonary TB screening.

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### OA-11-568-22 Identification and validation of Efflux pump Inhibitors against Rv1218c in Multi Drug Resistant Tuberculosis clinical isolates

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**Background:** Tuberculosis caused by *Mycobacterium tuberculosis* (Mtb) is a leading cause of death and increasing Multi-Drug Resistant (MDR-TB) strains is an increasing concern globally. Efflux pumps are one of the intrinsic mechanisms of resistance that acts as a permeability barrier to reduce the passage of antimicrobials across the bacterial cell wall. Increased efflux activity can occur in response to prolonged exposure to sub-inhibitory concentrations of anti-TB drugs. Rv1218c is a major ABC transporter which causes efflux of multiple substrates novobiocins and pyridines. One possible method to prevent resistance by efflux pump is to use efflux pump inhibitors which in turn increases activity of the antibiotics. In this study, we are interested in designing and validating inhibitors against MDR-TB efflux pump Rv1218c.

**Design/Methods:** The efflux pump gene Rv1218c from the clinical isolates was amplified and over expressed in *M. smegmatis* strains. The efficacy of the short listed small molecule inhibitors were validated through checker board combined with tetrazolium micro plate-based assay. Additionally efflux activity was further validated by a fluorometric method that uses ethidium bromide as efflux substrate.

**Results:** MICs of the shortlisted lead inhibitors against Rv1218c recombinant *M. smegmatis* remained high, but that of RMP in combination with the small molecular inhibitors reduced from 16 µg/mL to 0.5 for Raffinose and Palmitic acid respectively in the recombinant, demonstrating the potential nature of these inhibitors. Furthermore, Raffinose and Palmitic acid were validated for their efflux inhibition potency using ethidium bromide accumulation study. The accumulation of ethidium bromide inside the recombinant mycobacterium cell wall exhibits the efficiency of the lead compounds.

**Conclusions:** Findings through this study resulted in identifying Raffinose and Palmitic acid as a potent efflux pump inhibitor reducing the MICs of Rifampicin in the drug resistant clinical isolates considerably creating a window for the reintroduction of the crucial drug into the regimen treating MDR-TB patient.

### OA-12 Confronting TB stigma

#### OA-12-569-22 Why is TB called the 'Disease of Paper'? Exploring perceptions about the spread of tuberculosis in rural South Africa

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**Background:** Clear health communication between health workers and communities affected by tuberculosis can create a mutual understanding about preventing the spread of TB and address stigma.

**Design/Methods:** This qualitative research study included 18 health care workers (2 had previous TB disease) and 15 patients (9 had previous TB disease) and was based in a rural area in the Eastern Cape, South Africa. Semi-structured interviews were conducted in English and isiXhosa and lasted 30 to 90 minutes. Interviews were transcribed, translated and analysed inductively using thematic analysis.

**Results:** The isiXhosa term for tuberculosis, *Isifo Sephepha*, directly translates as 'the disease of paper'. Asking participants about the etymology of this term was a lens to examine connotations of TB as disease. Rich potential explanations from health workers and patients ranged from phonetic similarities to the word *phophezelayo*, 'to have a dry, irritating cough', to risk factors, including smoking cigarettes rolled with paper, and modes of spread, such as burning of paper or having a dirty home with papers lying around, or high risk occupations, including miners who receive referral papers or money with their TB diagnosis. Participants offered different explanations about how TB spreads via the air (through coughing, talking, dried sputum or dust). All participants were uncertain about the duration that someone with TB can continue to spread it to others. Other findings included community initiated social separation of persons with tuberculosis for the duration of treatment. This entails separate rooms, separate eating utensils and preventing contact with children. Health workers infrequently discussed perceptions about TB spread and how to prevent TB from spreading at home during health education, emphasising treatment adherence and contact investigation instead.

**Conclusions:** Understanding community perceptions of TB spread would assist health workers to adapt health education messages. This could avoid ineffective, prolonged or stigmatising infection prevention measures at home.

### OA-12-570-22 Characterizing tuberculosis stigma in the community: a mixed-methods study in Cambodia

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**Background:** Stigma is a significant barrier to healthcare and a factor that drives the global burden of tuberculosis (TB). However, there is a scarcity of information on TB stigma in Cambodia. We aimed to characterize and explore the determinants of TB stigma among people with TB in Cambodia.

**Design/Methods:** We conducted a mixed-methods study using a triangulation convergent design—a cross-sectional survey among 730 people with TB and 31 nested in-depth interviews. Characterization and assessments of the determinants of TB stigma included descriptive statistics and generalized linear regression models. Qualitative transcripts were thematically analyzed.

**Results:** A total of 56% and 51% of participants agreed or strongly agreed to all statements on the self-stigma and perceived stigma by the community scales, respectively. We found rural residence, knowledge of how TB is transmitted, and that anybody can get TB were associated with higher self- and perceived stigma by the community. Higher scores on knowledge of TB symptoms were inversely associated with both self and community stigma. Thematic analyses revealed accounts of experienced stigma, acts of intentional distancing and hiding TB diagnosis from others, and feelings of embarrassment and shame.

**Conclusions:** TB stigma was prevalent, suggesting a need for the incorporation of stigma reduction strategies in the national responses against TB. Future research should continue to characterize TB stigma in different populations through behavioral surveillance using standardized tools.

### OA-12-571-22 Tuberculosis-related stigma in urban communities in Uganda: what are the predictors?

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**Background:** According to the Uganda Tuberculosis patients cost survey report (2019), over 50% of tuberculosis (TB) patients in Uganda experience social exclusion due to TB-related stigma. TB-related stigma leads to TB diagnostic delays and treatment interruption which contributes to resistance to first-line drugs. The USAID-funded Defeat TB project sought to better understand TB-related stigma and its social demographic predictors in large urban centers in Uganda to guide design and implementation of stigma reduction interventions.

**Design/Methods:** In January 2019, the project conducted a cross-sectional study in three districts in central Uganda. The project sampled 164 TB patients systematically and 315 non-TB patients using Lot Quality Assurance Sampling (LQAS). These were interviewed using the Van Rie Stigma Likert Scale questionnaire. Respondents with a 66.7% score or higher were categorized as having TB-related stigma. Multiple logistic regression was used to examine associations between TB-related stigma and socio-demographics.

**Results:** Most respondents were female (61.8%), below 50 years old (84%), educated to secondary level (44.1%) and had low TB knowledge (43%). A proportion of 54.9% had TB-related stigma; 64.6% and 49.8% among TB patients and non-TB patients respectively. Having HIV-related stigma (OR 3.4, 95% CI 2.2, 5.4,  $p = 0.000$ ), being below 50 years old (OR 2.6, CI 1.5, 4.4,  $p = 0.000$ ), being a TB patient (OR 3.3, 2.1, 5.1,  $p = 0.001$ ), and being a TB patient with low TB knowledge (OR 3.6, 95% CI 1.5, 8.3,  $p = 0.003$ ) were positive predictors (risk factors) for TB-related stigma. Gender and education level were not associated with TB stigma ( $p > 0.05$ ).

**Conclusions:** Among study participants from these urban communities, TB-related stigma was higher among TB patients compared to non-TB patients. TB stigma reduction interventions should aim to reduce HIV-related stigma, target persons aged below 50 years, active TB patients and TB patients with low TB knowledge for greater impact.

## OA-12-572-22 Gender Differences in Perceived TB Stigma in Kampala, Uganda: A cross sectional analysis

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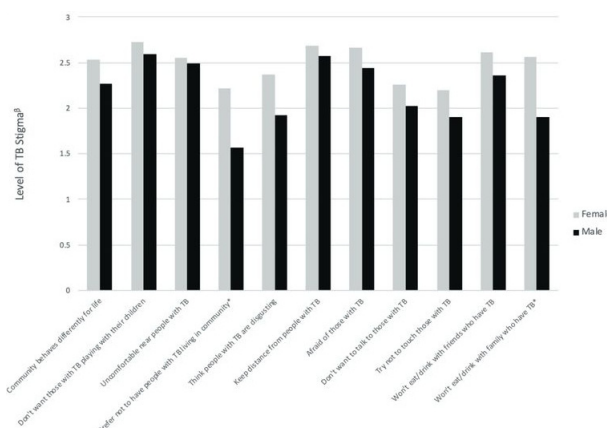
**Background:** Tuberculosis (TB) is stigmatized in many high-burden settings. Perceived stigma prevents individuals from engaging with TB diagnostic and treatment services. Men and women may differ in perceptions of or sensitivity to TB-related stigma. Therefore, we sought to compare perceptions of TB-related stigma among men and women at high risk for TB.

**Design/Methods:** We conducted a cross-sectional study of perceived TB-related stigma nested within a study offering HIV testing to TB household contacts at home. We enrolled consecutive index patients with  $\geq 2$  adult (age  $\geq 15$ ) contacts at two public health clinics in Kampala, Uganda. Community Health Workers (CHWs) visited homes of index patients and enrolled adult household contacts. CHWs recorded demographics, clinical information, and responses to Van Rie stigma scales for HIV and TB before HIV counseling and testing. We used random-effects Poisson regression with robust standard errors to estimate the effect of gender on perceived TB-related community stigma.

**Results:** Of 164 adult contacts enrolled, 103 (63%) were women. 15 (10%) were persons living with HIV. Median age was 27 (interquartile range (IQR) 20.5-40.5). The median perceived TB stigma score for men was 26 (IQR 20-30) and 30 (IQR 24-33) for women. Controlling for age and household clustering, women reported significantly greater perceived TB stigma than men (adjusted rate ratio 1.08, 95% CI 1.01-1.16,  $p=0.026$ ).

Women were significantly more likely than men to agree that people in the community viewed TB patients as disgusting ( $p=0.009$ ), that community members believed TB patients should not live in the community ( $p=0.001$ ), and that relatives would not share meals with TB patients ( $p=0.0001$ ).

**Conclusions:** Female contacts of TB patients perceived greater TB-related stigma than male contacts. Future TB programs aimed at engaging household contacts in TB care should be cognizant of ways in which stigma may affect women and should target destigmatizing interventions in ways that combat these perceptions.



[Figure 1. Individual questions on the Van Rie Stigma Scale by Gender.

$\beta$  On a scale of 0 to 3 for each individual question. Higher scores represent higher levels of stigma \*statistically significant difference by gender with a Bonferroni correction ( $p < 0.004$ )

## OA-12-573-22 A mixed-methods assessment of stigma in people living with drug-resistant TB and HIV in South Africa

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**Background:** Stigma contributes to poor health outcomes in both drug resistant TB (DR-TB) and HIV. In 2019-20, we assessed co-occurring stigmas related to DR-TB and HIV among coinfecting patients in KwaZulu-Natal, South Africa.

**Design/Methods:** An adapted 20-item stigma survey assessing DR-TB, HIV, and combined stigma was administered to 113 patient participants receiving antiretroviral and bedaquiline-based DR-TB treatment enrolled in the PRAXIS (Prospective Study of Adherence in M/XDR-TB Implementation Science) Study. In-depth interviews were held with 8 patients based on report/omission of enacted stigma. Consolidated and characterized survey data was triangulated with thematic analyses of interviews. Data collection is ongoing.

**Results:** Survey scores emphasized two factors, internal and enacted stigma, that loaded separately for DR-TB and HIV. DR-TB and HIV-stigma were significantly correlated ( $r=.621$  internal;  $r=.711$  enacted) and DR-TB stigma was consistently higher than HIV stigma. Scores for seriousness and risk to health were higher for DR-TB. Scores for community understanding about disease prevention and acceptance were higher for HIV. Interviews, convergent with survey data, suggested stigma was driven by “othering” and labelling patients as deviant, dangerous and defiant. Enacted stigma manifested as physical separation (distance, differentiation of personal items), severed inter-personal relations (rejection, refusal to visit/live with), name-calling (“low-life”, “burden”, “disgrace”, “use-less”), ignorance (inaction/lack of empathy), and attributed largely to DR-TB. Exclusionary acts cultivated anticipated stigma (fear of disclosure) and internal stigma that manifested as shame (unworthiness), self-blame (deserving of mistreatment), self-punishment (suicidal ideation) and, given concurrent fears of death, a self-concept that patients were non-contributing members of society and ultimately “disposable”.

**Conclusions:** Preliminary results identify substantial internal and enacted stigma, more for DR-TB than HIV, calling for greater individual and community awareness to mitigate DR-TB and HIV stigmas. Special efforts to manage community fears in ways that enable patient empowerment could facilitate their well-being and treatment success.

### **OA-12-574-22 “I hope we can do infection control in a more human way”: balancing safety and stigma in rural South African health facilities**

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**Background:** Stigma is an important barrier that limits access to TB care. TB infection prevention and control (TB IPC) measures are important to create safe health-care environments but may inadvertently contribute to TB stigma. We explored patient and health worker perspectives on TB IPC in health facilities.

**Design/Methods:** This qualitative research study was conducted at five facilities (primary and secondary level care) in a rural area in the Eastern Cape, South Africa. Participants included 18 health care workers (2 had previous TB disease, 3 facility managers, 4 health workers leading TB care in their facilities) and 15 patients (9 had previous TB disease). Interviews were conducted in

English and isiXhosa, lasted between 30 and 90 minutes, and used a narrative approach with semi-structured interview guides. Interviews were translated, transcribed and analysed inductively using thematic analysis.

**Results:** Participants described receiving a mask as denoting the moment someone is diagnosed with TB. Masks have become a visual symbol of TB disease (for some drug-resistant TB) that other patients and health workers can see.

Some health workers reported that they stopped using masks and respirators for TB IPC to prevent patients from feeling stigmatised. Patients also reported negative connotations with mask wearing, but accepted it as important to keep health workers and other patients safe. The importance of communal well-being or ‘ubuntu’ was weighed stronger than individual discomfort.

Suggestions from participants on how to implement TB IPC in a person-centred way include providing clear explanations, paying additional attention to non-verbal communication, acknowledging someone’s role in the community when addressing them and implementing universal mask-wearing in health facilities.

**Conclusions:** TB IPC practices may conflict with person-centred care, yet play a critical role in ensuring safety in health facilities. Developing messaging that clearly explains TB IPC and emphasise communal wellbeing and safety could assist with addressing TB stigma.

### **OA-12-575-22 Funding human rights programs in the TB response: the Global Fund experience**

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**Background and challenges to implementation:** Since 2017, the Global Fund intensified its support the countries to fund evidence-based and quality programs to address human rights-related barriers to access. While the uptake of the human rights programs has been slow in TB, in the last funding round saw around 1000% increase in the funding level for human rights programs.

**Intervention or response:** Stigma, discrimination, breach of medical confidentiality and informed consents are some of the most frequently identified human rights-related barriers to accessing TB services.

Despite that NSPs increasingly highlight the importance of addressing human rights access barriers, there is still a limited understanding of evidence-based programs to address those barriers and how those programs can be integrated as part of the TB response. The Global Fund in conducting an in-depth funding analysis to understand the inclusion of the human rights programs in the TB grants in the 2017-2019 funding cycle.

The analysis examine how the applicants have identified the human rights-access barriers in the funding applications, in line with their NSPs; to what extent those

barriers are addressed through concrete programs with clear budgets; and document the efforts to measure the impact of those programs.

**Results/Impact:** The analysis shows that there has been a significant increase in the number of the funding applications clearly identifying human rights barriers to TB services; and funding concrete programs to address those barriers. Yet, such investments and programs often focus HIV/TB co-infection; and there is a limited focus on TB-specific human rights programs. Nonetheless, there are countries, notably, Ghana, Mozambique and DRC, where specific efforts led to the integration of the human rights programs in the community-led TB programs, providing important lessons to share.

**Conclusions:** The analysis aims to develop a comprehensive Global Fund funding landscape for human rights programs in TB; and identify best practices to better support the countries.

### OA-12-576-22 The development and validation of a scale to measure stigma and in people with drug-resistant tuberculosis

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**Background:** Tuberculosis (TB) stigma contributes to diagnostic delay, disease concealment and reduced well-being for affected individuals and their communities. According to the World Health Organization (WHO), Vietnam is a high TB and multidrug-resistant (MDR)-TB burden country, where the effects of stigma may affect patient care. Stigma-reduction interventions are challenging to evaluate due to a lack of validated scales to measure stigma in this population. This study aims to develop and validate a scale to measure stigma in patients affected by MDR-TB.

**Design/Methods:** An initial 45-item stigma scale was developed based on a review of the literature, 19 qualitative interviews and 37 cognitive interviews. The scale was further developed and validated in patients with MDR-TB across four provinces in Vietnam. Psychometric analysis for the scale included exploratory and confirmatory factor analysis, internal consistency, content validity, construct validity and test-retest reliability.

**Results:** Of the 358 patients with MDR-TB invited to participate in the study, 315 provided written consent and completed the self-administered survey (a response rate of 88.0%). Factor analysis identified 14 items across four sub-scales associate with MDR-TB stigma including, guilt, social exclusion, physical isolation and blame.

The goodness of fit indices were acceptable (GFI=0.94, NNFI=0.89, CFI=0.92, RMSEA=0.058 and SRMR=0.062). Internal consistency was acceptable (Cronbach's Alpha=0.76), test-retest reliability was good (ICC=0.92), and construct validity showed a positive mild correlation ( $r=0.27$ ) with depressive symptoms and a negative mild correlation ( $r=-0.28$ ) with quality of life. **Conclusions:** This scale demonstrated satisfactory psychometric properties for measuring stigma associated with patients with MDR-TB.

### OA-13 The race for improved multidrug-resistant care

#### OA-13-577-22 Best practices in bedaquiline and delamanid use for RR-TB management: implementation of extension and combination use in 43 high burden countries

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**Background and challenges to implementation:** Since 2017, the World Health Organization (WHO) recommended extension beyond 24 weeks and combination use of bedaquiline (Bdq) and delamanid (Dlm) for select drug-resistant TB (DR-TB) cases. Accumulated evidence on best practices will inform updated guidance forthcoming in 2020 WHO Consolidated Guidelines. Information on the status of extension, combination, and paediatric use of the novel agents at country level is needed.

**Intervention or response:** The #StepUpforTB 2020 study aims to assess policy-adoption of best practices for TB diagnosis, prevention and treatment in 43 high TB burden countries by end December 2019. A semi-structured questionnaire was used to interview National TB Programme managers or assigned focal points and supplemented by a desk review of national policy documents. The overall response rate was 84%.

**Results/Impact:** The use of Bdq and Dlm for routine treatment of DR-TB is limited to 24 weeks in 21/36 countries. In 28/36 countries, Bdq may be used from aged 6 years and above, while in two countries the youngest al-

lowable age is 12 years and in one country 18 years.

The youngest allowable age for the use of Dlm is 3 years in most countries (24/36), while for three countries it is 6 years. The combined use of Bdq and Dlm is allowed for routine DR-TB treatment in 25/36 countries, with half the countries (17/36) allowing it for up to 24 weeks. 10/36 countries report that the combined use of Bdq and Dlm is not indicated in national policies or research protocols and 1/36 country allows its use under operational research settings.

**Conclusions:** 69% of countries surveyed recommend combination use of bedaquiline and delamanid, while only 40% of countries allow routine extension of bedaquiline and delamanid. While recommended for children at younger ages, adoption of best practices in bedaquiline and delamanid for adults remains slow.

### OA-13-578-22 The decentralised drug-resistant TB programme in South Africa: from policy to implementation

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**Background:** A policy supporting decentralised drug-resistant (DR)-TB treatment provision was introduced in South Africa in 2011, but implementation has varied in different settings. Drawing on the Policy Triangle framework, this paper sought to examine how content, actors and processes of policy interact in context-specific ways to inform implementation.

**Design/Methods:** The research employed a multiple case study design in two provinces, KwaZulu-Natal and the Western Cape. Qualitative methods included interviews with 90 MDR-TB experts, health policymakers and implementers at national, provincial and local levels; supplemented by a review of documents. Thematic analysis was utilised.

**Results:** Stakeholders shared different interpretations of the goals of decentralisation and had strong and divergent views about the appropriateness of decentralising DR-TB. This resulted in contestation regarding policy priorities and differences in the models of service delivery implemented.

Contextual factors that inform decentralisation of DR-TB care include political pressure, the culture within the programme, challenges related to multilevel governance, and resource allocation for implementation.

Actors influence implementation positively and negatively, through their perceptions and organisational politics, and the presence of champions and resisters of change. Policy champions were motivated to implement national policy. Programme or quality champions seemed to resist decentralisation but were passionate about DR-TB and had concerns that decentralisation would negatively affect quality of care.

The process of policy implementation bypassed district structures resulting in a lack of ownership. Provinces and districts also did not plan in a way that anticipated service delivery challenges, resource needs and mechanisms for clinical governance. There is a tension between achieving coverage of decentralisation and maintaining quality of care.

**Conclusions:** As South Africa moves towards bold and progressive new treatment policy, we need to learn from lessons over the past ten years. This paper presents an understanding of policy dynamics which will contribute lessons for strengthening future implementation of DR-TB policy.

### OA-13-579-22 Programmatic management of MDR/XDR-TB patients using the short treatment regimen from 2015 to 2019 in Cameroon

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**Background and challenges to implementation:** Since its official approval by the World Health Organization (WHO) in 2015, Cameroon has been using the so-called “Bangladesh regimen” to manage all patients with Rifampicin-Resistant and Multidrug-Resistant Tuberculosis patients (RR/MDR-TB) under a programmatic management.

**Intervention or response:** Data from patients receiving the short injectable-containing regimen from 2015-2019 were collected using an Epidata-base software. We review the national database describing the treatment success rate per year, the occurrence of side effects and TB second line resistance.

**Results/Impact:** A total of 706 patients were started on the injectable-based regimen during 2015 to 2019 with a median age of 35 [27-82] years old. Males patients represented 445 (63%); lung localization of the disease was the most common site in 674 (96%) cases. Upon treatment initiation, 216 (31%) cases were found to be HIV positive and 682(97%) were never exposed to second line anti-tuberculosis treatment. From the 380 (54%) patients with available initial second line probe assay results, 10 (3%) were found to be resistant to fluoroquinolones and 15 (4%) resistant to second line injectable. Favorable outcome was observed for 505 (82%) patients versus 109 (18%) for those with unfavorable outcomes. More specifically, we had a total of 76 (12%) death cases, 27 (4%) loss to follow-up and 6 (1%) patients were declared treatment failure. A total of 478 (68%) patients had a documented adverse events, the most represented moderate to severe event concern the auditory system in 57 (12%) cases followed by the hepatic system in 18 (4%) cases.



Out of those presenting an auditory event, second degree was observed in 32 (56%) and 25 (44%) patients with a 3rd degree.

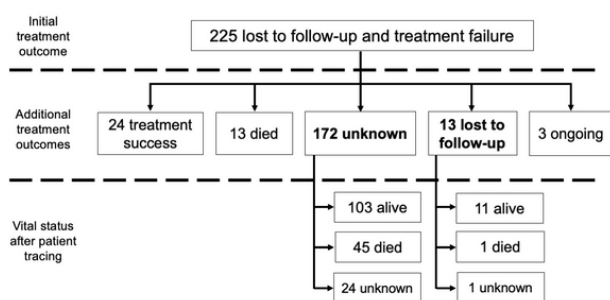
**Conclusions:** Programmatic management of RR/MDR-TB using the short treatment regimen has shown good results for the past five years in Cameroon. Nevertheless, the occurrence of a 57 (12%) poor auditory outcomes remain the major challenge and need a more closer monitoring of patients audiogram by health personnel in charge.

### OA-13-580-22 Outcomes of a representative sample of patients lost to follow-up during drug-resistant tuberculosis treatment in the Philippines

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**Background:** Loss to follow-up is common among patients being treated for drug-resistant TB and may bias estimates of mortality and program success. We traced patients lost to follow-up from the Philippines National Tuberculosis Control Program (NTP) to determine their vital status and ultimate TB treatment outcome.

**Design/Methods:** All pre-XDR/XDR-TB patients diagnosed and a random 1:1 sample of MDR-TB patients treated through the Philippines NTP from 2013-2016 were included (N=683). Patients with an original treatment outcome recorded as lost to follow-up (n=203) or treatment failed (n=22) were traced by searching the NTP electronic database to identify additional episodes of care, calling patients up to three times on separate days using the listed patient's and emergency contact numbers, and/or conducting a home visit to the most recent address with assistance from local public health staff. Patients successfully traced were interviewed regarding their current health status and TB treatment history. If immediate community members were contacted, only vital status information was collected.



[Figure 1.]

**Results:** Of the 225 patients with an original treatment outcome of lost to follow-up or treatment failed, 53 had additional treatment episodes (24 successfully treated, 13 died, 13 lost to follow-up, 3 ongoing treatment) (Figure 1). Of the 185 with no additional treatment episodes or who were lost to follow-up again, 114 (62%) were found to be alive, 46 (25%) died, and 25 (14%) were unable to be traced.

Overall, 200/225 (89%) patients were successfully traced, of whom 59 (26%) died. After tracing, the known mortality rate increased from 12% (80/683) to 20% (139/683), a difference of 9% (95% CI 6-11).

**Conclusions:** Tracing drug-resistant patients lost to follow-up identified additional mortality. Strategies for minimizing loss to follow-up and conduct of post-treatment follow-up of patients are critical in improving NTP outcomes and reporting accurate mortality data.

### OA-13-581-22 Undiagnosed drug resistance in Mycobacterium tuberculosis is associated with higher mortality in countries with high tuberculosis burdens

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**Background:** Drug-resistant Mycobacterium tuberculosis (Mtb) strains threaten tuberculosis (TB) control. We compared results from (i) drug resistance testing at clinics in high TB burden countries (Xpert MTB/RIF, line probe assay or culture), (ii) standardized drug susceptibility testing (DST) performed at the Swiss National Center for Mycobacteria (liquid culture) and (iii) whole genome sequencing (WGS).

**Design/Methods:** We collected Mtb isolates from adult TB patients in Ivory Coast, Democratic Republic of the Congo, Kenya, Nigeria, South Africa, Peru, and Thailand, stratified by HIV status and TB drug resistance in 2013-2016. We sequenced and screened the strains with Illumina HiSeq 2500 and TBprofiler. We compared drug resistance profiles and used multivariable regression (adjusted for sex, age, HIV status, history of TB, sputum microscopy, and TB lineage) to assess the impact of undiagnosed drug resistance on mortality.

**Results:** We included 582 TB patients: median age 33 years (interquartile range: 27-43), 225 (39%) female, and 247 (42%) HIV-positive. Based on WGS, 332 (57%) isolates were pan-susceptible, 33 (6%) mono-resistant, 148 (25%) multidrug-resistant (MDR-TB), and 26 (4%) pre-extensively or extensively drug-resistant (pre-XDR/

XDR-TB). All testing methods identified isoniazid and rifampicin resistance with high concordance. Resistance to ethambutol, fluoroquinolones and injectable drugs were often undiagnosed at local laboratories (Figure). Local DST and WGS were discordant in 156 (27%) cases. Among these results, 73/156 (47%) were under-diagnosed and 83 (53%) over-diagnosed. The odds ratio for mortality was 3.03 (95% CI 1.7-6.42) if they were under-diagnosed, and 1.18 (0.46-2.66) if over-diagnosed compared to patients with concordant results.



[Figure. Distribution of diagnosed drug resistance with different drug susceptible testing methods.]

INH, isoniazid; PZA, pyrazinamide; EMB, ethambutol; RIF, rifampicin, FQL, fluoroquinolones including ofloxacin, levofloxacin and moxifloxacin; INJ, injectable including streptomycin, amikacin, capreomycin, kanamycin; “nd class orals including para-aminosalicylic-acid, cycloserine, ethoinamid; 3rd class orals including bedaquiline and clofazimine.

**Conclusions:** We observed discrepancies between the DST profiles obtained at local laboratories, the reference laboratory and WGS, particularly for second-line drugs. These discrepancies can result in inadequate treatment and consequently higher mortality. WGS can provide accurate and detailed drug resistance information, which is necessary to improve the management of drug-resistant TB in high burden settings.

**OA-13-582-22 Predominant yield of drug sensitive tuberculosis among contacts of multi-drug resistant tuberculosis patients in Uganda: a call for next generation sequencing**

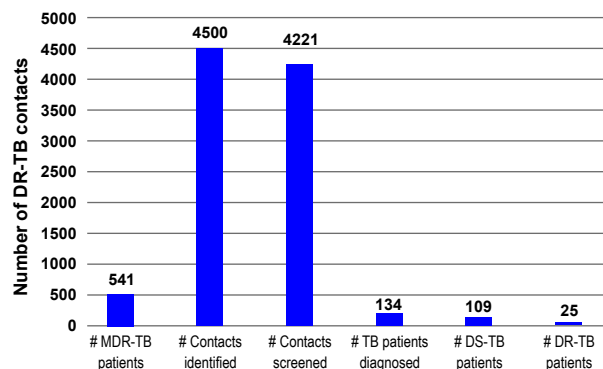
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**Background and challenges to implementation:** Early detection and treatment of multi-drug resistant tuberculosis (MDR-TB) is critical to reducing disease transmis-

sion, incidence, and mortality. Identifying and screening contacts of index TB patients is one strategy for early TB diagnosis. The Uganda Ministry of Health guidelines for contact investigations recommend screening all contacts of confirmed MDR-TB patients at initiation of treatment and thereafter, at least every six months for all contacts. The USAID Defeat TB project provides technical assistance for programmatic management of drug resistant TB to the 17 regional referral hospitals that provide MDR-TB services including contact investigation activities. The project analysed the MDR-TB contact investigation cascade to determine the TB yield and the gaps for improvement of the cascade.

**Intervention or response:** From January to December 2019, all 17 MDR-TB treatment hospitals traced household and close contacts of patients diagnosed with MDR-TB. Data on the number of contacts completing each step of the cascade was recorded in health facility registers. During February 2020, the project abstracted this data and performed a descriptive analysis of the numbers and proportions completing each step of the cascade.

**Results/Impact:** During the review period, a total of 4,500 household and close contacts of 541 MDR-TB patients were identified. Of the 4,221 (93%) evaluated for TB, 134 (3%) were newly diagnosed with TB. Of those newly diagnosed TB patients, 109 (81%) had drug-susceptible TB (DS-TB) while 25 had drug-resistant TB (Figure 1).



[Figure 1. MDR-TB contact investigation cascade]

**Conclusions:** The findings confirm that contact investigation is a feasible strategy for active TB case finding in the community. The predominant yield of DS-TB among contacts of probably points to greater community than household transmission and merits further inquiry. We recommend the scale up of DR-TB contact investigation and further studies including next generation sequencing to explain the observed yield of DS-TB.

### OA-13-583-22 Achieving high treatment success rate for drug-resistant tuberculosis following introduction of the novel shorter treatment regimen

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**Background:** Despite significant milestones in global tuberculosis (TB) control, treatment success rate among multidrug-resistant tuberculosis (MDR-TB) patients has remained low. The World Health Organization (WHO) updated its treatment guidelines for drug-resistant TB in 2016, to include recommendations on use of novel injection-based shorter treatment regimens, and thereafter in 2019, to phase out injection-based regimens in favor of all-oral treatment.

In April 2018, Uganda adopted a shorter, nine to eleven-month regimen and enrolled patients based on the WHO eligibility criteria. USAID Defeat TB sought to determine estimates of successful (cure, completed or both) and poor (death, failure and lost to follow up) treatment outcomes among patients enrolled into the shorter regimen in 2018.

**Design/Methods:** USAID Defeat TB conducted a retrospective data review of medical records of 388 patients started on MDR-TB treatment at all 17 drug-resistant treatment initiation centers in Uganda between April and December 2018. The data was extracted from a DHIS-2 based database managed by the USAID-funded Defeat TB project. The project assessed treatment outcomes for bacteriologically confirmed rifampicin resistant (RR-TB) and MDR-TB patients. The project also used treatment outcome definitions and classifications included in the 2016 updated WHO treatment guidelines.

**Results:** Of the 388 medical records reviewed, 176 (45.4%) patients were found to be on the shorter regimen and included in the evaluation. Of the 176 patients, 54 (30.7%) were female. The median age was 36 years. The final treatment outcomes were as follows: 125 (71%) patients were cured, 14 (8%) completed treatment, 17 (9.7%) patients died, 8 (4.5%) patients were lost to follow up, and 12 (6.8%) patients experienced treatment failure.

**Conclusions:** 79% of the patients on the shorter regimen were treated successfully which compares favorably with the national target of 80%. The case fatality rate remained high (9.7%). Further research to evaluate and mitigate drivers of mortality would be of interest.

### OA-13-584-22 Introducing facility-based mortality reviews into programmatic management of drug-resistant tuberculosis: lessons from Uganda

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**Background:** Reducing tuberculosis (TB) deaths is one of the World Health Organization's End TB Strategy targets. Death among multi-drug resistant TB (MDR-TB) patients in Uganda remains high (>19%). The USAID Defeat TB project supported 17 treatment initiation facilities to pilot facility-based mortality reviews.

**Design/Methods:** USAID Defeat TB developed a mortality case review form to capture demographic and clinical data for patients who died between 2016 and 2019. Teams at the 17 treatment initiation facilities conducted a combined 79 mortality reviews between June 2018 to December 2019 to review cause of death, identify patient and system factors for improvement.

**Results:** Of the 79 deaths, 39.2% (31) were female with a median age 35 (interquartile range [IQR] 30-43) years. 35.4% (28) were multi-drug resistant, 63.3% (50) were rifampicin resistant and 1.3% (1) patient had extended resistance to injectables. Poor treatment adherence (missed  $\geq 30$  doses) was reported in 26 (32.9%) patients. 55.7% (44) of the deaths occurred within the first two months. 64.6% (51) patients had HIV-related comorbidities with only 86.3% (44) of the HIV co-infected on ART. 13.9% (11) patients had non-HIV comorbidities namely; acute malnutrition (5), diabetes (2), deep venous thrombosis (1), cancer (1), kidney (1) and liver diseases (1).

Possible system factors contributing to death included; delays in diagnosis among 58.2% (46) patients who had symptoms longer than one month prior to seeking care and delays in enrollment among 48.1% (38) patients that did not start treatment until after 7 days. Drug toxicity was reported in 15.2% (12), of which 7 (58.3%) were serious.

**Conclusions:** More than two thirds of the patients had comorbidities and died within two months of enrollment. Delays in diagnosis and linkage, poor adherence and drug adverse events contributed to death. We recommend institutionalization of mortality reviews into drug-resistant TB care to continually identify and address drivers of mortality.

## OA-14 COVID-19: the great disrupter

### OA-14-585-22 The contribution of asymptomatic SARS-CoV-2 infections to transmission - a model-based analysis of the Diamond Princess outbreak

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**Background:** Some key gaps in the understanding of SARS-CoV-2 infection remain. One such gap is the extent to which individuals experiencing asymptomatic infections contribute to transmission, an essential input for estimating the impact of social controls, including physical distancing. We aimed to estimate the proportion, infectiousness and contribution to transmission of individuals with asymptomatic infections during the outbreak on the Diamond Princess cruise ship.

**Design/Methods:** We used a transmission model of COVID-19 with asymptomatic and presymptomatic states, calibrated to outbreak data from the Diamond Princess, to infer the contribution to transmission of individuals with asymptomatic infections. Data used for inference included the date of symptom onset for symptomatic disease in passengers and crew separately, the number of symptom-agnostic tests administered each day, and the dates that asymptomatic and presymptomatic individuals tested positive.

**Results:** On the Diamond Princess 74% (70-78%, 95% credible interval) of all infections proceeded asymptotically, translating to a 1:3.8 case-to-infection ratio. Despite intense testing, 53% (51-56%) of infections remained undetected, most of them asymptomatic. Asymptomatic individuals were the source for 69% (20-85%) of all transmission. While the data did not allow identification of the infectiousness of asymptomatic infections, assuming no or low infectiousness resulted in estimates for the net reproduction number of an individual progressing through both presymptomatic and symptomatic stages in excess of 15.

**Conclusions:** Asymptomatic SARS-CoV-2 infections may contribute substantially to transmission. This is essential to consider when assessing the potential effectiveness of ongoing control measures to contain COVID-19, particularly social controls such as physical distancing.

## OA-14-586-22 Effect of COVID-19 on tuberculosis patient notification in Japan

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**Background:** The spread of COVID-19 and related political and social responses, such as the declaration of emergency and various restrictions may affect tuberculosis (TB) infection or TB disease. In addition, much of the work of medical institutions, local governments, and public health centers is being devoted to COVID-19 response, and there is a concern that it may compromise TB control activities.

**Design/Methods:** We compared and analyzed the number of notifications of TB cases from January to March of 2019 and 2020, using the monthly report of TB surveillance in Japan.

**Results:** The number of newly notified TB patients in the first quarter of 2020 was 2,999, which represented a 10% decrease compared with the first quarter of 2019. The numbers of smear-positive pulmonary TB patients and latent tuberculosis infection were 1,158 and 410 respectively, each representing a 16% and 25% decrease. As for the mode of detection, the number of TB patients detected at health checkups in school declined from 25 to 14, a decrease of 44%.

In addition, the number of TB patients detected via contact investigation decreased from 174 to 95, a 45% decrease. In particular, those detected via contact investigation for non-family members showed a substantial decline of 59%, from 111 to 46.

**Conclusions:** There was a slight decrease in the number of newly notified TB cases in the first quarter of 2020, as compared to the same period of 2019[K1]. However, the substantial reduction in the number of patients detected via contact investigation, especially for non-family members, was worrying. This may be due to an increase in the burden of COVID-19 related work at public health centers, as well as to contacts of TB patients refraining from undertaking medical examinations.

## OA-14-587-22 Contacts or care? Impact of COVID-19-related disruption on tuberculosis burden

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**Background:** The impact of COVID-19-related disruptions on TB services is a serious cause for concern. Health systems overload and stay-at-home notices could severely affect health-service availability and access for TB detection and treatment. However, social distancing could limit *M.tb* transmission. We estimated the combined effect of COVID-related health-service disruption and social distancing on TB burden in China, India and South Africa.

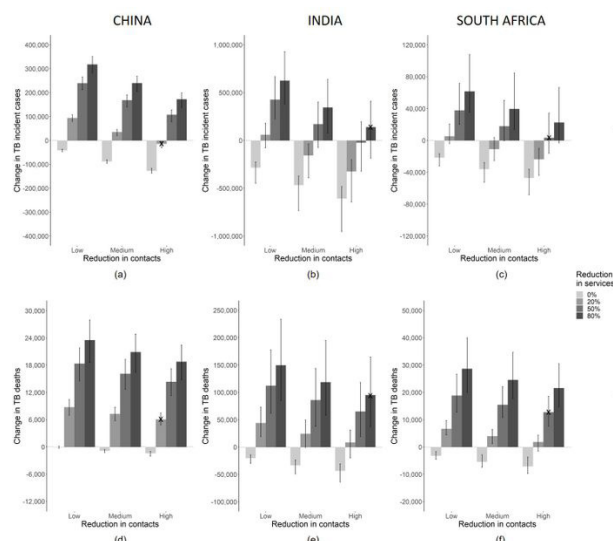
**Design/Methods:** Using an *M.tb* transmission model with age-specific contact matrices calibrated to data from the three countries, we explored three scenarios for social contact reduction and for TB service disruption (Low/Mid/High). Age-wise contact patterns were reweighted, reflecting larger reductions in contacts in schools, transport, and leisure settings, and smaller reductions in workplaces.

Health service disruptions were modelled as reductions in both the proportion of incident cases detected and successfully treated. Reductions were implemented early 2020 for 6-months. We estimated 5-year cumulative change in TB incidence and deaths compared to no-change baseline.

**Results:** Over five years, the potential benefit of social distancing is likely to be larger for TB incidence than TB deaths. However, in scenarios with substantial health service disruption, we projected an increase in both cases and deaths, regardless of the level of social distancing.

In our worst case scenario, as many as 201,595 (range:123,523 - 301,553) additional TB deaths could occur across China, India, and South Africa over 5-years. However, if countries minimise impact on TB health services, major reductions in social contacts could help minimise additional TB deaths.

**Conclusions:** Overall impact depends on the balance between health-service disruption and social distancing. However, any benefit of social distancing on TB deaths is likely to be outweighed by health-service disruption. It is crucially important to maintain and strengthen TB-related health services during, and after, the COVID-19 pandemic.



[Figure 1: Five-year cumulative change (median & range) in TB incidence(a-c) and deaths(d-f) resulting from COVID-related social and/or health system disruption.]

## OA-14-588-22 The impact of the COVID epidemic on Active TB Case Finding (ACF) interventions in Nigeria: The KNCV TB Foundation Nigeria experience

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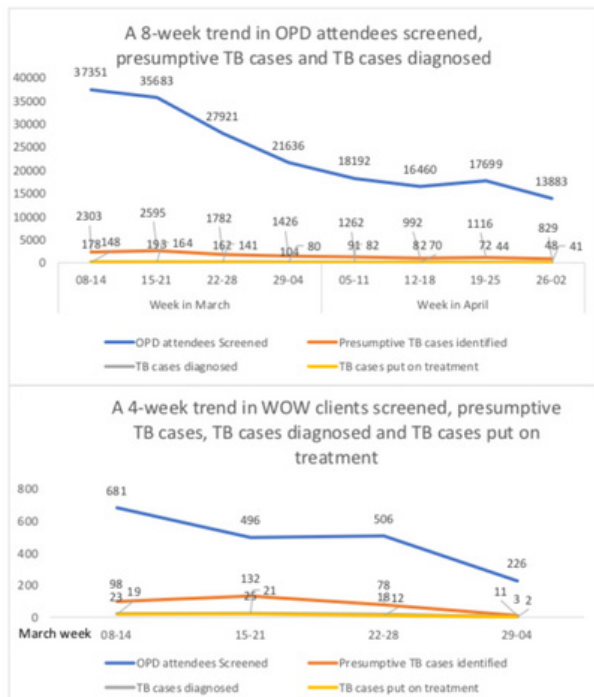
**Background and challenges to implementation:** The National TB program had embraced Active TB Case Finding strategies to address the increasing gap in TB case finding. KNCV TB foundation rolled out two high impact active TB case finding interventions; the TB Surge across 61 high volume facilities in 9 states and the WoW campaign in Kano State from Jan 2020. The first case of COVID was diagnosed in Nigeria on the 27th of February 2020.

**Intervention or response:** The TB surge intervention supports the engagement of ad hoc staff for routine TB screening, presumptive TB identification, referral for diagnosis, and linkage to DOTS. The WoW is a mobile diagnostic unit (MDU) housing a digital X-ray machine and 2 four-module GeneXpert machines that deliver screening and diagnosis to the doorstep of the people at risk for TB. Data along the TB cascade are recorded for all clients using the CommCare app and collated for analysis every week.

With the advent of the COVID epidemic, we provided training to staff on infection prevention and control (IPC) and supplied personal protective equipment including N95 masks.

The NTBLCP guideline on TB implementation in the era of COVID was adapted and used in the training of health care workers.

**Results/Impact:** We observed a progressive decrease of 63%, 64%, 73%, and 72% in Clinic attendance, presumptive TB identification, TB cases detected, and treatment initiation respectively for the TB surge and 67%, 89%, 87%, and 89% in client's enrollment, presumptive TB identification, TB cases detected and treatment initiation for the WoW interventions since the onset of the COVID epidemic in Nigeria. See Fig 1.



[Figure 1. Trends in OPD TB screening, presumptive TB identification and TB treatment; TB surge and WoW campaign, KNCV Nigeria March - April 2020]

**Conclusions:** The COVID epidemic has impacted negatively on TB case finding in Nigeria. Innovations in TB programming such as the use of digital health technology should be intensified to support patients and programs through improved communication and information management at this time.

**OA-14-589-22 Willingness to test for TB amongst symptomatic community members in an era of COVID-19: findings from an exploratory mixed-methods study from Anambra State Nigeria**

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**Background:** Based on national government directives Anambra state in south-east Nigeria implemented widespread control measures against the COVID-19 pandemic on 23rd March. These included: lockdown of movements in the state, closure of businesses, schools, places of worship and private businesses as well as mandatory isolation for anyone suspected to have the disease. On 10th April 2020, the state recorded her first confirmed COVID-19 case. Routine TB program monitoring data showed a significant decline in the number of Xpert MTB/RIF sputum tests done in April compared to the monthly average from January to March. This work explores the possible impact of the COVID response on willingness to test for TB.

**Design/Methods:** An electronic mixed-methods survey was designed and sent to community linkage coordinators (LCs). The LCs are employed to collect sputum samples from community members and patent medicine vendor (PMV) outlets in the state. Thematic analysis was applied to the qualitative component which sought to gauge the attitude of community members with symptoms of TB towards undergoing TB tests.

**Results:** 18 linkage coordinators responded to the survey. 90% reported a negative change in attitude towards TB testing since the advent of COVID-19. Further, 61% reported that PMVs seemed unwilling to collect sputum samples from symptomatic clients for TB testing. Increased transport costs, lack of basic PPEs at the PMV outlets and prevailing (mis)understanding of public health information affected the number of sputum samples available for testing.

Although the enforced movement restrictions affected the ability of persons to access care at health facilities, a strong theme of fear emerged from the data. Community members expressed apprehension towards TB test for fear of being diagnosed with COVID-19 and subsequently forced into isolation and separation from family.

**Conclusions:** The communication of interventions instituted for the COVID-19 response affected the willingness of symptomatic community members towards TB testing.



## OA-14-590-22 Use of virtual -and community delivery- platforms to prevent MDR-TB treatment interruption during the national COVID-19 response: lessons from Uganda

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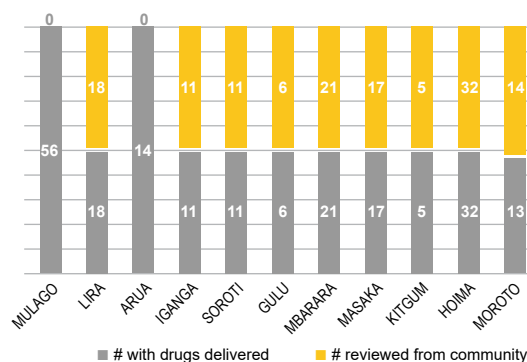
**Background and challenges to implementation:** Following WHO's declaration of the COVID-19 outbreak a pandemic on 11th March 2020, Uganda government instituted prevention measures through a national wide lock-down on 24th March 2020 to mitigate the spread of COVID-19. As a result, many patients with Multi-drug resistant (MDR-TB) couldn't attend their monthly hospital reviews for clinical- and laboratory- assessment. We assessed the situation affecting delivery of MDR-TB services and instituted remedial interventions.

**Intervention or response:** In response to the national wide lock-down, the USAID Defeat TB project with the national TB and leprosy program (NTLP) held virtual meeting with all MDR-TB treatment initiation centers to plan continuation of care. The following interventions were agreed and implemented:

- Conducted virtual education about COVID-19
- increased provision of personal protection equipment (PPE) to health care workers
- deployment of community treatment supporters to ensure continuity of directly observed treatment (DOT)
- expansion of community-based care to sustain monthly clinical reviews and sputum monitoring
- provision of adherence support through weekly phone calls to all patients
- drug deliveries to all DOT sites to maintain adequate stock.

**Results/Impact:** Over 100 healthcare workers were oriented on TB/COVID-19 integration, infection prevention and control and provided with N95 respirators and face masks. A total of 204 patients attended their monthly clinic reviews and had their drugs restocked. Of these 135 (66%) had their clinical reviews carried out in the community (fig 1). Two newly diagnosed MDR-TB patients were also linked to care. No contact tracing was done to minimize community contact.

**Conclusions:** The use of virtual platforms together with community-based patient reviews and drug deliveries ensured continuity of care for patients with MDR-TB during the COVID-19 outbreak in Uganda. We recommend consolidation of the virtual coordination and community service delivery platforms for to optimize provision of DR-TB care.



[Figure 1. MDR-TB drug deliveries and patient community reviews for select sites (7-22 April 2020)]

## OA-14-591-22 Implementation of psychosocial support services for patients with tuberculosis during the quarantine regime due to Covid-19

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**Background and challenges to implementation:** Quarantine will limit the spread of COVID-19, although this may adversely affect patients living with tuberculosis (TB). In response to the emergency, the Ukraine National TB program and the Project reformatted their activities to ensure continuous access to TB treatment and psychosocial support for vulnerable groups of patients. **Intervention or response:** Approaches to organizing the provision of services to customers have been changed.

In project management:

- project management is carried out remotely using online platforms and CRM systems;
- organization of distance learning of project managers in NGOs and social workers;
- regular online meetings with medical institutions and NGOs, partners.

In the organization of the provision of services to NGO clients:

- delivery of TB treatment by social workers and ART delivery for patients with co-infection (TB/HIV);
- remote control of TB treatment using gadgets;
- provision of personal protective equipment for social workers who continue to control DOT to patients with a high risk of separation from treatment;
- provision of transportation of biomaterials of clients for diagnostics;
- delivery of TB treatment drugs by mail, by courier;
- a mobile application has been developed for patient online registration in medical hospitals in the national medical system.



**Results/Impact:** - The risk of contracting a patient with TB has decreased (May 1, 2020 - 1 case of TB / Covid-19 was registered);

- cases of illness among social workers are not reported;  
 - the introduction of online communication made it possible to quickly respond to emerging problems with the involvement of central authorities.

**Conclusions:** Reformatting the project is expected to reduce the risks of the spread of Covid-19 among patients with TB.

Establishment of an alternative remote project management system can be used in such interventions and in emergency situations

The introduction in the future of flexible approaches for the psycho-social support of TB patients.

## OA-15 TB preventive therapy: we need to do better

### OA-15-592-22 Reaching at risk groups with TB Preventive Therapy (TPT). Building on commitments made at the United Nations High Level Meeting (UNHLM)

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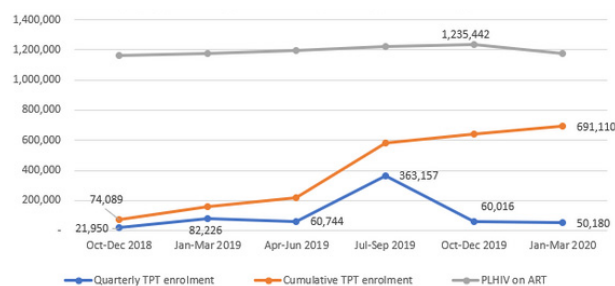
**Background and challenges to implementation:** The second commitment of the UNHLM Political Declaration on Tuberculosis (TB) is to reach 30,000,000 at risk people with preventive treatment by 2022. By September 2018, Uganda's TPT coverage was 4% among people living with HIV (PLHIV) & 14% among <5-contacts. Outlined below are the lessons & results from Uganda's TPT scale up & retention experience.

**Intervention or response:** The country endorsed the UNHLM declaration, lobbied for additional commodities for TPT and engaged high level leadership of the Ministry of Health which established a national TPT task force (HIV & TB programmes & partners). It engaged recipient of care networks to disseminate TPT messages & integrated TPT into a national HIV Quality Improvement (QI) Collaborative.

It issued TPT targets & allocation lists to support initial phased scale up followed by rapid TPT scale up, and integrated TPT reporting into a weekly online national HIV surge dashboard, and held monthly TPT perfor-

mance review meetings with stakeholders. To strengthen TPT completion, the supply chain for isoniazid was paired with pyridoxine; reserved 6-months of TPT commodities for each enrolled person; dispensed TPT & ART medicines jointly; monthly monitoring ± redistribution of TPT commodities; peer educators engaged to support adherence; scaled up drug safety monitoring & management; and disseminated quality improvement packages.

**Results/Impact:** TPT coverage improved between September 2018 & March 2020 among PLHIV from 4% (52,139/1,167,819) to 56% (691,110/1,235,442) and among <5-contacts from 14% (6,333/44,412) to 32% (7,416/23,469) respectively. TPT completion among PLHIV improved from 70% (13,419/19,103) in October - December 2018 to 90% (269,021/243,298) in January - March 2020.



[Figure. Graph showing TPT scale up among PLHIV in Uganda]

**Conclusions:** Bringing together all the health system building blocks including leadership & stakeholder engagement, leveraging existing resources coupled with employing a highly transparent TPT results accountability mechanism can greatly improve TPT coverage. The above-mentioned interventions are recommended for TPT scale-up other high burden settings.

### OA-15-593-22 TB preventive therapy policies in high TB burden country countries to achieve UNHLM TB targets

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**Background and challenges to implementation:** The 2018 United Nations High Level Meeting (UNHLM) set ambitious targets for the rapid scale up of testing and treatment for latent TB infection (LTBI). World Health

Organization (WHO) guideline updates on TB preventive treatment (TPT) were released in March 2020; information on country level adoption of current guidance is lacking.

**Intervention or response:** The #StepUpforTB 2020 study aims to assess policy-adoption of best practices for TB diagnosis, prevention and treatment in 43 high TB burden countries by the end of December 2019. A semi-structured questionnaire was used to interview National TB Programme managers or assigned focal points and supplemented by a desk review of national policy documents. The overall response rate was 84%.

**Results/Impact:** Before the provision of TPT, LTBI testing is not indicated for people living with HIV and contacts under five years in 15/36 countries. LTBI testing is indicated for contacts over five years in 8/36 countries. Half of countries (18/36) indicate tuberculin skin testing, while 11 and 2 indicate IGRA and Diaskin/C-Tb, respectively. National policies in 22/36 countries indicate a shorter regimen for TPT, with the majority including 3HP and 3RH and only 3 countries including 4R.

Most common reasons reported for not including shorter TPT regimens in policies are lack of funding for procurement and implementation (training, policy and document revision).

Two countries indicated they are not aware of WHO recommendations for shorter LTBI regimens. 8/36 countries indicate in their policies a levofloxacin-containing LTBI regimen for contacts of DR-TB patients.

**Conclusions:** Despite low access to IGRA, LTBI testing prior to provision of TPT is lessening as a policy barrier to implementation, and 60% of countries are recommending use of shorter TPT regimens. Countries will need to continue ambitious LTBI policy guidance to accelerate progress towards UNHLM targets by 2022.

### OA-15-594-22 Uptake of isoniazid preventive therapy among newly diagnosed people living with HIV initiating antiretroviral therapy in South Africa: a post-hoc analysis of a cluster-randomized trial

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**Background:** Isoniazid preventive therapy (IPT) reduces risk of incident TB disease and death among people living with HIV (PLHIV), yet uptake has been sub-optimal in South Africa (SA). Until recently in SA, a tuberculin skin test (TST) was required to determine IPT duration. The

use of TST has been identified as a barrier to IPT delivery; thus, we conducted a cluster-randomized trial to evaluate whether the Quantiferon-gold in-tube test (QGIT) to identify patients with TB infection could increase uptake of IPT among newly diagnosed PLHIV in SA.

**Design/Methods:** In this post-hoc analysis comparing QGIT clinics to standard of care (TST) clinics, we included only those participants initiating ART within 30 days of enrolment. Participants were followed for a maximum of 1-year post-enrolment via medical records to determine IPT initiation. We present the cluster-adjusted proportion of participants starting IPT, stratified by arm, and difference in IPT uptake with 95% confidence interval (CI).

**Results:** Across 14 clinics, 1,511 PLHIV starting ART within one month were included; 814 from QGIT clinics and 697 from TST clinics. 25% of participants were male and 34% were pregnant women. The median (IQR) age at enrolment was 31 years (25-38) and the median (IQR) baseline CD4 count was 305 cells/mm<sup>3</sup> (177-471). 70% of participants in the QGIT arm had a test conducted compared to 9% in the TST arm.

Approximately 66.1% of participants in QGIT clinics started IPT within one year compared to 40.4% of participants in TST clinics; a difference of 25.7% (95% CI: 0.1%-51.5%).

**Conclusions:** There was an approximate 26% increase in one-year IPT initiation in QGIT vs TST clinics among PLHIV starting ART. Though TB preventive therapy is now recommended for all PLHIV in SA, these results suggest that a systematic measurement of TB infection during routine blood draws for PLHIV could be an effective strategy for increasing IPT uptake.

### OA-15-595-22 Systems approach to improve Tuberculosis Preventive Therapy outcomes among people living with HIV in resource limited settings: Experiences from East-Central Uganda

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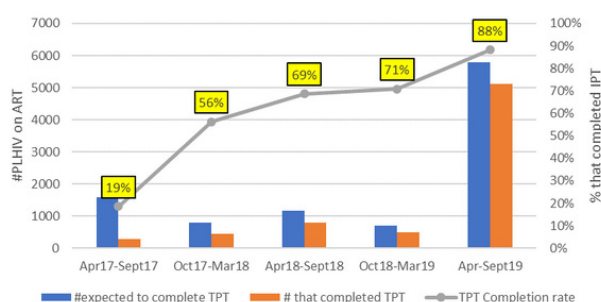
**Background and challenges to implementation:** Isoniazid Preventive Therapy (IPT) is a proven effective intervention to reduce the burden of TB among PLHIV.

However, IPT completion rates have often been poor in Sub-Saharan Africa (73% in an East-African study) and only 19% in the East-Central region of Uganda as of September 2017. USAID's RHITES-EC project supported health care workers (HCWs) at 100 facilities providing HIV care services to improve completion rates using quality improvement (QI) approaches to address barriers and root causes to sub-optimal IPT completion. Health system barriers included frequent stockouts of Isoniazid, poor coordination between IPT and ART de-

livery, knowledge gaps among HCWs, and poor data quality. Patient level barriers include lack of knowledge and negative side effects.

**Intervention or response:** Using the QI plan-do-study-act (PDSA) approach, the project supported HCWs to implement changes to address barriers for TPT completion by; committing six-month doses for each client to avert treatment interruption, integrating and synchronizing IPT delivery with ART delivery, including differentiated community ART delivery models. Facility-based training for HCWs were conducted to improve data quality, analysis, and clinical skills, including counseling clients on the importance of IPT and how to manage side effects.

**Results/Impact:** A trend analysis for IPT completion rates for semiannual cohorts for the period April 2017 to September 2019 was done. In the cohort of April-September 2019, a completion rate of 88% was achieved, compared to 19% completion rate in the baseline cohort of April-September 2017.



[Figure 1. Trend of TPT completion rates for semi-annual periods April 2017-September 2019]

**Conclusions:** Using QI methods can be effective in improving IPT completion rates in resource limited settings by addressing health system barriers, such as gaps in health workforce skills and knowledge, commodity stockouts, and poorly coordinated service delivery. QI methods can also be used to address patient level barriers to improve their ability to manage side effects.

### OA-15-596-22 Increasing access to TB preventive treatment for children under-five in DRC: preliminary results

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**Background:** Child contacts of TB cases are at high risk of infection and developing active TB disease. Despite the World Health Organization recommending household contact investigation (HCI) as critical to TB control, this intervention remains poorly implemented. In collaboration with a local civil society organization (CSO), we developed an effective model for systematic HCI and demonstrated its role in case finding and access to TB preventive treatment (TPT).

**Design/Methods:** We implemented systematic community-based HCI in 21 purposefully-selected health facilities in 10 health zones in Kinshasa, DRC. Key strategies of the intervention included: training community health care workers (CHWs) on pediatric TB screening, introduction and use of the contact register, mentorship of CHWs, and ensuring free access to TB services (TB Diagnosis, TPT, TB treatment) for all child contacts under age 5. EGPAF provided training on contact investigation and pediatric TB screening to CHWs, while the local CSO was involved in the planning, organization, and implementation of project activities. CHWs screened all children aged 0-14 years old who were members of TB index case households. Asymptomatic under-five contacts were considered eligible for TPT and referred to the facility for treatment initiation. Symptomatic children 0-14 years old were referred to facilities for diagnostic investigation. Data were collected through February to December 2019 using project forms.

**Results:** HCI screened 5,501 children, enabling the identification of 149 (2.7%) TB cases and 2,431 (44.2%) children eligible for TPT. Among TPT-eligible children, 96.6% (2,348) were successfully linked to treatment.

**Conclusions:** HCI contributes to pediatric TB case detection and access to TPT for children. Involvement of local CHWs, free access to facility-level services for child contacts referred from community-level services, close follow-up of child referrals, and mentorship/supportive supervision are key elements for the success of this intervention.

### OA-15-597-22 Interferon-gamma cytokine concentration levels as a biomarker for recent infection with mycobacterium tuberculosis in an African community setting

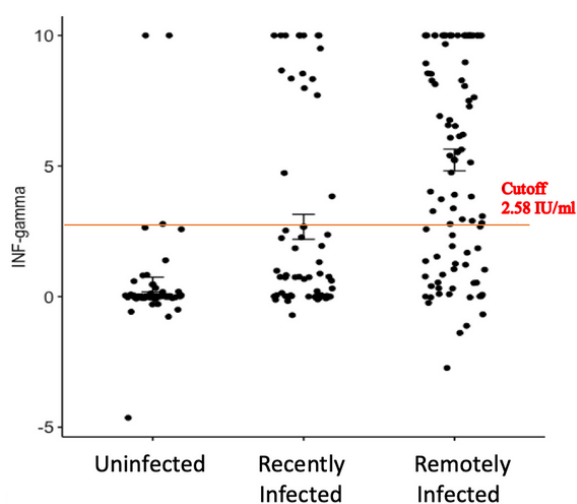
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**Background:** Recent infection with Mycobacterium tuberculosis is a major risk for the progression of infection to active disease. Little progress has been made to identify this population, who are a priority group for tuberculosis preventive therapy (TPT). We aimed to determine whether concentrations of Interferon- $\gamma$  cytokine could

serve as a biomarker to distinguish individuals that are recently infected with Mtb from uninfected and remotely infected adults in the community.

**Design/Methods:** From a cohort of adult residents in Kampala, Uganda followed up to two years, we identified three comparison groups: 55 subjects TST negative (<5mm) at baseline and negative at the last follow-up (uninfected), 64 subjects TST negative at baseline and TST positive ( $\geq 10$  mm) at the last follow-up (recently infected) and 97 subjects with a baseline TST positive (previously infected). Measurement of Mtb specific antigen induced interferon- $\gamma$  concentrations in blood was done using the QuantiFERON-TB Gold In-Tube test for all the study groups and Area Under the Curve analysis was used to assess for diagnostic performance characteristics.

**Results:** When accounting for background interferon- $\gamma$  levels, recently infected individuals had a higher mean interferon- $\gamma$  level (2.5 IU/ml) compared to uninfected individuals (0.46 IU/ml) yet had lower mean levels than previously infected individuals (5.12 IU/ml; Figure). Interferon- $\gamma$  measurement resulted in the correct classification of 69% of recently infected individuals compared to previously infected individuals using an optimal cut-off value of 2.58 IU/ml with a sensitivity of 73% and specificity of 67%.



[Figure: Graph shows optimal cutoff value of 2.58 IU/ml from Area Under Curve analysis value of 69%.]

**Conclusions:** Concentrations of interferon- $\gamma$  after stimulation with Mtb-specific antigens could serve as a biomarker to discriminate recently infected from remotely infected groups despite having the same mean TST reading in an African community setting. If validated, this approach may help to prioritize for TPT.

## OA-16 TB Xpert in low- and middle-income countries: ensuring quality and quantity

### OA-16-598-22 Phased scale up of External Quality Assurance (EQA) for GeneXpert MTB/RIF testing under National TB Elimination Program (NTEP), India

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**Background and challenges to implementation:** India rapidly scaled up GeneXpert MTB/Rif testing almost doubling the sites (628 to 1180) and increasing testing by five times (578,173 to 2,407,211) from 2016 to 2018. To ensure that the entire testing process (pre-analytical, analytical, and post analytical) is quality assured it was planned to implement an External Quality Assurance Program (EQAP) in 2018 by the National TB Elimination Programme (NTEP) in collaboration with National Tuberculosis Institute (NTI), Foundation for Innovative New Diagnostics (FIND), Centers for Disease Control and Prevention (CDC) and World Health Organization using CDC's dried tube specimen technology. The EQAP was piloted at 41 sites in 2018 and scaled up to cover 622 sites in 2019.

**Intervention or response:** Indigenous capacity to manufacture Proficiency Testing (PT) panels was built at NTI by training 2 staff at CDC Atlanta followed by in-country training of 16 staff.

The step wise implementation of EQAP includes:

- 1) Standardization of SOP to achieve 100% panel stability and consistency.
- 2) Development of data collection, monitoring and analysis tools.
- 3) Engaging and training the National and Intermediate Reference Laboratories (NRLs and IRLs) for implementing and monitoring EQAP.
- 4) Training of GeneXpert sites by respective NRLs and IRLs.
- 5) Arrangements for packing and transporting of panels (using India Post).

**Results/Impact:** Capacity for manufacturing PT panels was successfully scaled up from 50 to 725 in a year and is currently >1500.

EQA was implemented in phased expansion from 41 sites to 622 sites. Over 97% sites scored satisfactorily (Table 1). Corrective actions were taken at all 12 sites with unsatisfactory PT results. 11 sites showed significant improvement in phase III.

	Phase I (Feb-Mar 2018)	Phase II (Jul-Aug 2018)	Phase III (Mar-May 2019)
In country manufacturing of PT panels (set of 5 tubes)	50	230	725
No. of States/UTs involved	3	4	20
No. of Districts involved	32	123	398
No. of NRL/IRL participated	1/1	1/3	3/19
No. of sites participated	41	199	622
No. of machines participated	41	212	664
Sites with satisfactory (>80%) results (No. and %)	41 (100%)	198 (99.5%)	609 (97.9%)
Sites with unsatisfactory (<80% scores) results (No. and %)	0	1(0.5%)	13(2.1%)
Sites with at least one discrepant result (No)	1	12	60

[Table 1.]

**Conclusions:** Proper planning, capacity building, monitoring, and improvising has enabled India's NTEP to successfully implement one of the largest GeneXpert EQA programs in the world.

### OA-16-599-22 South Africa's Xpert MTB/RIF Ultra EQA experience - need for good laboratory practice to minimize contamination

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**Background:** By March 2018, South Africa had transitioned from Xpert® MTB/RIF to Xpert® MTB/RIF Ultra (Ultra) due to improved sensitivity. The transition involved 203 laboratories with 325 GeneXpert systems. Quality assurance is monitored using the SmartSpot Quality external quality assurance (EQA) panels, distributed thrice yearly. Each panel comprises four dried culture spots for testing. Responses are submitted via an on-line portal with assessments based on 2/2(100%) if correct result is reported, 0/2(0%) if incorrect, and 1/2(50%) for reporting of an unsuccessful or rifampicin (RIF) indeterminate result. An analysis of EQA performance, post transition to Ultra, was performed.

**Design/Methods:** Ultra EQA data was extracted from the SmartSpot Quality submission portal and analysed using Microsoft excel. Data was segregated by system serial number, EQA panel identifier, panel score, expected and reported results.

**Results:** For 2018, 780 EQA panels (3120 samples) were tested with Ultra. 95.6% of results yielded 100% pass rate. Incorrect results (including those scored at 50%) reported in 137/3120 (4.4%): 77.4% due to discordant

results, 18.2% instrument/assay errors, 4.4% RIF indeterminate results. Reasons identified for discordant expected results were contamination of EQA specimens during processing and inadequate specimen mixing, these consist of a notable increase in expected negative results reported as trace or positive and some expected positive results reported as Negative.

Possible contamination detected among 8.8% of discordant results expected to yield positive results with rifampicin detected as either sensitive instead of resistant or vice versa.

**Conclusions:** Due to Xpert® MTB/RIF Ultra's increased sensitivity, improving stringency of techniques during specimen handling and processing, maintaining good laboratory practice, and adhering to standard operating procedures (SOPs) is critical in minimizing contamination. Areas of concern should be addressed through observation of testing procedures and training.

### OA-16-600-22 Mentoring TB labs for improving and sustaining QMS implementation and ISO 15189 accreditation: experiences from India

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**Background and challenges to implementation:** In 2016-17, Foundation for Innovative New Diagnostics (FIND) in collaboration with India's National TB Programme (NTP) supported 11 TB laboratories to improve their quality management systems (QMS) and achieve ISO 15189 accreditation from National Accreditation Board for Testing and Calibration Laboratories (NABL).

**Intervention or response:** Baseline assessments were conducted in Feb-Mar2017 using FIND's TB laboratory quality management systems towards accreditation harmonized checklist-v2.1. Subsequently, the labs were provided intensive mentoring through workshops and onsite visits to implement QMS and prepare towards NABL accreditation over 10-18 months. The labs underwent NABL assessments and achieved accreditation in 2017-18. The labs were followed up and provided need-based support to sustain QMS post accreditation.

Follow-up assessments were conducted using same checklist at these 11 NABL accredited sites in Oct 19 - Feb 20 to review their progress, identify gaps and measure quality improvements made since baseline assessments.

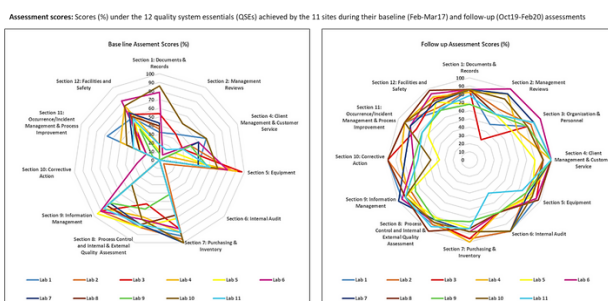


**Results/Impact:** All 11 sites successfully achieved NABL accreditation. Mentoring support through FIND helped the labs in fast-tracking their preparations.

Baseline and follow up assessment scores were compared to quantify QMS implementation. Improvement was seen in all areas with significant changes seen in documentation (38% to 81%), management reviews (13% versus 71%), organization and personnel (44% to 83%), internal audits (1% to 81%), client management and customer satisfaction (35% to 95%). Overall, 8/11 (72%) sites improved and sustained quality with total scores >85%, remaining sites scored between 75-85%.

However, few labs lagged in effectively implementing corrective actions, occurrence management, management reviews, etc. although they had improved scores in follow-up assessment. Action plans were prepared for each site and the labs are rectifying their lacunae.

**Conclusions:** With commitment, motivation, monitoring and hand holding, it is possible to improve and sustain quality of lab services and NABL accreditation. ISO 15189 accreditation gives confidence to the program about quality, timeliness and reliability of diagnostics results from these laboratories.



[Figure.]

## OA-16-601-22 A pilot study on the implementation of proficiency testing dried tube specimen production at National Public Health Laboratory-National Tuberculosis Laboratory, Kenya

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**Background:** The National Public Health Laboratory (Tuberculosis Reference laboratory) has received dried tube specimen (DTS) external quality assurance (EQA)

panels for Xpert MTB/RIF assay from the US Centers for Disease Control and prevention (US-CDC) since 2014. To ensure 100% coverage among Xpert MTB/RIF testing facilities in Kenya, NTRL requested for technology transfer of DTS production the US-CDC. The NTRL was mentored to produce DTS and successful transfer was demonstrated through pilot EQA panels.

**Design/Methods:** The technology transfer started with a readiness assessment of NTRL Kenya in August 2018, followed by panel production training at Supranational National Reference Laboratory-Uganda (SRL-UG) in January 2019 and onsite mentorship in June 2019 at NTRL. As part of competency assessment, NTRL enrolled 20 facilities for DTS testing. Facilities received, tested and returned results. US-CDC and SRL-UG trainers in training provided onsite mentorship in result evaluation from participating facilities, online reporting, and DTS production processes by reviewing the panel validation data while identifying areas for improvement. In the second pilot, 50 facilities were enrolled country-wide.

We describe herein the results of the two pilot rounds.

**Results:** Of the 20 facilities enrolled in the first pilot, 20/20 (100%) responded with 16/20 (80%) facilities scoring 100% while 3/20 (15%) scored less than 100% but above the 80% pass mark and 1/20(5%) failed. The second pilot, 50 sites enrolled, 48/50 (96%) responded, 36/48 (75%) scored 100%, while 7/48(15%) scored less than 100% but above the 80% pass mark and 4/48(8%) failed.

The rate of sites scoring satisfactory ( $\geq 80\%$ ) or better in both pilots was 95% and 92% with concordance of 95% and 96% respectively. One facility consistently failed due to transcription error in both pilots.

**Conclusions:** NTRL demonstrated competency for DTS production and EQA program and CAPA management. NTRL to consider scaling this program to all testing facilities.

### OA-16-602-22 Role of GeneXpert technology in early detection of Rifampicin Resistant tuberculosis in Afghanistan

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**Background and challenges to implementation:** Elimination of tuberculosis (TB) is a major health priority for the world and Afghanistan. Multidrug-resistant tuberculosis (MDR-TB) poses enormous challenges to health systems due to the complexity of diagnoses and treatment.

The current landscape for TB response underscores the urgent need for rapid diagnosis to control TB, especially in resource-limited settings.

In 2014, National TB Program (NTP) introduced GeneXpert technology in Afghanistan and installed the first GeneXpert machine in Kabul for detection of Rifampicin Resistant (RR) patients and gradually increased number of machines in the country.

In 2019, 45 GeneXpert machines installed in 25 provinces by NTP, Challenge TB (CTB) and Global Fund (GF).

**Intervention or response:** NTP develop GeneXpert and sample transportation guidelines, assessment tool, posters and registers. NTP conducted GeneXpert training for 100 laboratory technicians and 25 Provincial Laboratory Supervisors (PLS) to use the machines. NTP regularly supplied cartridge to all GeneXpert sites and conducted supportive supervisory visits form mentioned sites.

The technical team reviewed the available surveillance data to identify the role of GeneXpert in detection of RR TB cases in the country.

**Results/Impact:** As a result; in 2017, 7542 tests performed from that 6522 (86%) test was MTB cases detected our all 279 (3.6%) RR patents were detected in 10 GeneXpert sites in 10 provinces, while in 2019, 52783 tests performed from that 16154 (30.1%) test was MTB cases detected, so our all 486 (1 %) RR patents were detected in 45 GeneXpert sites in 25 provinces.

Variables	2017	2018	2019
Number of GeneXpert Machines	10	32	49
Number of GeneXpert tested	7542	17153	52783
Number of RR detected	279 (3.6%)	445 (2.5%)	486 (1%)
Number of MTB detected	6522 (86%)	13734 (80%)	16154 (30.1%)
Number of RR detected among presumptive TB and new Bacteriological conform TB cases	151	254	265
Number of RR detected among previous treated TB cases	128	191	221

[Table.]

**Conclusions:** By smooth implementation of GeneXpert technology, we succeeded to detect more RR patients and put on treatments. We recommend expanding this technology to more sites and bring easy access to detect RR patients.

### OA-16-603-22 Overcoming barriers to GeneXpert optimization in Nigeria: an analysis using the Access concept

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**Background:** With the adoption of GeneXpert machine by WHO in 2010; Nigeria commenced the rollout plan in 2011 and by the end of 2019, 407 GeneXpert machines had been installed with the aim of improving TB diagnosis including Rifampicin resistant TB. Despite this number, only 59% of all TB cases in 2019 got tested with GeneXpert. There is still an enormous gap in optimizing utilization of GeneXpert. This study examined the barriers to GeneXpert optimization and proposes approaches to overcome them.

**Design/Methods:** Desk review of 2019 GeneXpert data was conducted. A qualitative case study approach was used to generate data on GeneXpert human resources (HR)' experiences in providing services. Using interview guides, in-depth interviews were conducted with 45 purposively selected Xpert HR from sites that performed an average monthly test of 240 and above and 39 sites that performed below 150 tests monthly. This was triangulated with the views of 23 TB program managers via key informant interviews. Interviews were audio-taped and transcribed. Thematic content analysis was guided by Penchasky and Thomas Access framework: availability, acceptability, affordability and accessibility.

**Results:** Barriers were mainly availability and accessibility factors - skewed distribution of available GeneXpert machines, Inadequate human resources (HR), poor maintenance and frequent breakdown of machines, irregular power, cartridge supply interruptions, low demand for GeneXpert testing. Optimization package to



overcome barriers include -establishment of specimen transport mechanisms, use of ad hoc GeneXpert HR, training of 'super-users' for prompt machine maintenance and minor repairs, installation of solar panels, repair/prompt replacement of power accessories, supply chain strengthening, demand creation through active case finding activities.

**Conclusions:** The study highlighted the complexities that influence realistic optimization of GeneXpert and ways to surmount them. It is imperative that the design of GeneXpert optimization interventions integrates approaches to overcome potential constraints for effective TB control in Nigeria.

### OA-16-604-22 The use of Xpert MTB/RIF in mobile vans: experience from Namibia

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**Background and challenges to implementation:** Namibia is a high-burden tuberculosis (TB) country in Southern Africa. Since 2017, Xpert MTB/RIF® has been the primary diagnostic test for TB in Namibia. The first time Xpert MTB/RIF occurred outside a formal laboratory, however, was during the recent TB prevalence survey. We present our experience using GeneXpert systems in mobile vans as part of field-based TB screening activities.

**Intervention or response:** As part of a nationally representative, population-based, TB prevalence survey, participants >15 years old underwent symptom screening, chest radiography (CXR), followed by sputum collection and Xpert MTB/RIF testing as per international guidelines. Eight four-module GeneXpert systems installed in four mobile vans (two in each) travelled across the country during the survey. Power for the instruments was provided mainly from the municipal power grid with intermittent solar power and petrol generators in the absence of power. Four trained technologists operated the instruments. Sample quality checks immediately followed collection according to the manufacturer's specifications.

**Results/Impact:** We enrolled 29,525 participants. Of those, 10,884 (36.9%) were eligible for sputum collection; with 9,512 (87.4%) Xpert test performed in the field. Each field-based machine performed an average of 1,189 tests. In all, 116 (1.2%) patients tested positive for M. tuberculosis. Thirty-three invalid results occurred during the survey (3.5 errors per 1,000 tests). A majority of invalid results (61%) presumed to be the result of a malfunctioning air conditioning system in a single van.

**Conclusions:** Namibia's experience showed that Xpert MTB/RIF testing in mobile vans was feasible and may be used for field-based screenings. Trained operators,

well-functioning vehicles and quality samples ensured that 87% of eligible participants received valid TB results in less than one day.

### OA-17 Safety first: side effects of old and new drugs

#### OA-17-605-22 Title: Audiometry outcomes during and after DR-TB treatment with a kanamycin containing drug-regimen, DR-TB patients assessed in 3 rural districts of Masvingo Zimbabwe

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**Background and challenges to implementation:** Second-line anti-TB injectables (SLIs) used in the treatment of drug-resistant tuberculosis (DR-TB) are a known cause of hearing loss. SolidarMed (SM), an organisation in health working in partnership with the Zimbabwean Ministry of Health (MoHCC), supports (DR)TB services in 3 districts in Masvingo. We share audiometry screening experiences and findings among DRTB-patients managed within these districts.

**Intervention or response:** All patients treated with a kanamycin containing DRTB treatment regimen between 2013-2019 were identified and tracked by TB focal persons using MoHCC TB registers and invited to come for screening at the district hospital with transport being reimbursed. Clinical, otoscopic and audiometric assessments using the HearTest™ audiometer were carried out by trained personnel from September 2019 onwards. Results were uploaded to hearX cloud and analysed.

**Results/Impact:** Of 60 patients identified, 35(58%) came for screening. The majority (88%) were aged >15yrs, female (51%), and HIV positive (63%). None of the patients had a previous audiometric assessment, while 40% had finished their DRTB treatment. On audiometry examination, 12(34.3%) had profound hearing loss in both ears requiring cochlear implants; of these, 5(42%) were still on treatment. Sixteen (46%) patients with moderate hearing loss in at least one ear required hearing aids and discontinuation of kanamycin. Patients with no or mild hearing loss received a monitoring schedule. Tinnitus was the main presenting complaint in patients with hearing loss, accompanied by headaches.

**Conclusions:** Lack of audiometry monitoring in rural Zimbabwe has led to undetected hearing loss among DRTB patients treated with kanamycin. Introduction of the portable audiometer enables the districts to follow

recommendations on audiometry assessments, while the use of SLI in the management of DRTB is currently phased out in the country. Post-treatment audiometry in patients who never had audiometry before can be useful to manage quality of life using hearing aids and possibly occupational therapy.

### OA-17-606-22 Validation study comparing tablet-based and conventional audiometry results in stage 2 of the STREAM trial

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**Background:** Injectable aminoglycosides used for treatment of multidrug-resistant tuberculosis (MDR-TB) may cause irreversible hearing loss. Access to conventional audiometry is limited or unavailable in some settings with a high burden of tuberculosis. Tablet-based audiometry was used to monitor hearing loss amongst STREAM stage 2 trial participants; it was compared to conventional audiometry.

**Design/Methods:** Tablet-based and conventional audiometry testing were done in parallel for trial participants between April 2018 and November 2019. Both testing platforms measured pure tone audiometry in decibels at 1000, 2000, 4000, 6000 and 8000 Hz. Hearing loss was graded according to Brock's Criteria. Sensitivity and specificity of tablet-based audiometry, and a Kappa-statistic assessing level of agreement between the two testing methods were calculated for each ear.

**Results:** In total, 105 (537) participants had 217 (2330) conventional (tablet-based) audiometry results available at the relevant frequencies. After matching exactly on test date, 126 pairs of results (in 56 participants) from Uganda (59%), South Africa (38%), India (2%) and Mongolia (1%) were available for comparison. Of these, 10 tests (6 left, 4 right) could not be graded and seven tests (4 left, 3 right) were excluded as the results indicated errors in the test, leaving 116 and 119 paired test results for the left and right ear respectively. Tablet-based audiometry had high sensitivity (94% left, 100% right) and specificity (93% left, 94% right).

The results, using Brock's criteria, agreed for 91.4% (118/116) of left ear and 95.8% (114/119) of right ear pairs. Kappa-statistics for both ears showed substantial agreement between the two tests ( $\kappa = 80.1$  for right ear and  $\kappa = 91.2$  for the left ear).

**Conclusions:** Tablet-based audiometry was a sensitive tool for detecting hearing loss and an effective way to monitor clinical trial participants; it should be considered in settings where conventional audiometry is limited or unavailable.

### OA-17-607-22 Safety and efficacy of a shorter TB treatment - TTP as a surrogate marker of bacterial load in an RCT of high-dose rifampicin and pyrazinamide

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**Background:** Tuberculosis (TB) treatment is long, posing risk of poor treatment adherence. We aim to investigate a strategy to shorten TB treatment by exploring safety, and efficacy of higher doses of rifampicin (RIF) and pyrazinamide (PZA) on early bactericidal activity (EBA) using time to culture positivity (TTP) in BACTEC 960 MGIT (MGIT).

**Design/Methods:** Adult patients with pulmonary TB admitted to five hospitals in Sweden and subjected to receive first-line TB treatment are included. Patients are randomized to either 6-month standardized TB treatment (n=10) or a 4-month regimen (n=30) based on high-dose RIF (35 mg/kg) and PZA (40 mg/kg) along with standard doses of isoniazid (INH) and ethambutol (EMB).

Plasma samples for measurement of drug exposure determined by liquid chromatography tandem-mass spectrometry (LC-MS/MS) are obtained at 0, 1, 2, 4, 6, 8, 12 and 24 h day 1 and week 2. Maximal drug concentration ( $C_{max}$ ) and area under the concentration-time curve ( $AUC_{0-24h}$ ) are estimated by non-compartmental analysis. Conditions for early therapeutic drug monitoring (TDM) of high-dose RIF/PZA are explored by model-based analysis. Potential adverse effects are monitored throughout study. EBA is assessed by TTP in MGIT of induced sputum collected at day 0, 5 and week 1, 2 and 8.

**Results:** Preparing steps with a standard curve was developed by comparing TTP to CFU counts on Middlebrook 7H10 medium showing a linear correlation between CFU counts and TTP levels. A pilot study (n=7) exhibited a steady and significant prolongation of TTP during standard treatment of drug-susceptible TB (median delta TTP 16 hours/day for week 0-1).

**Conclusions:** TTP is strongly linked to the bacillary load with the potential to reflect drug efficacy and early clinical improvement during TB treatment. This phase II-study will provide knowledge on safety and EBA in relation to drug exposure of a shorter high-dose RIF/PZA regimen compared with standard TB treatment.

### OA-17-608-22 Predictive analyses of QT prolongation from ECG monitoring in STREAM Stage 1

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**Background:** STREAM Stage 1 was a randomised non-inferiority phase 3 trial comparing a 9-month “short” regimen versus standard of care for MDR-TB patients. The primary safety outcome was occurrence of a  $\geq$ Grade 3 adverse event; this included a corrected QT interval (QTc)  $\geq$ 500 milliseconds (ms) (associated with cardiac arrhythmia). More QTc prolongation events occurred in the short regimen, likely due to high-dose moxifloxacin and clofazimine. We explored whether there was a cut-off value that could allow prioritisation of ECG monitoring, potentially useful in programmatic settings with limited resources.

**Design/Methods:** Trial participants on the short regimen who developed QT/QTcF  $\geq$ 500ms on treatment were identified. QT/QTcF measurements at baseline, 4 hours post first dose, weeks 1-4 and 12 were investigated to determine whether patients who developed QT/QTcF  $\geq$ 500ms could be predicted. Fisher’s exact test was used to compare the proportion of patients developing QT/QTcF  $\geq$ 500ms to those that did not.

#### Results:

Time point post randomisation	QTcF	Prolongation $\geq$ 500ms (n=30)	Total	Sensitivity	Specificity	
4 hours	<415ms	3(2.5%)	120	90%	47.95%	
	$\geq$ 415ms	27(17.5%)	154			
	<425ms	5(3.0%)	169	83.33%	67.21%	
	$\geq$ 425ms	25(23.8%)	105			
	<430ms	9(4.68%)	192	70%	75%	
	$\geq$ 430ms	21(25.61%)	82			
	<435ms	13(5.9%)	220	56.67%	84.84%	
	$\geq$ 435ms	17(31.5%)	54			
	<445ms	18(7.2%)	249	40.00%	94.67%	
	$\geq$ 445ms	12(48.0%)	25			
	Week 3	<415ms	1(1.12%)	89	83.33%	54.32%
		$\geq$ 415ms	5(6.33%)	79		
<425ms		1(0.85%)	118	83.33%	72.22%	
$\geq$ 425ms		5(10%)	50			
<430ms		1(0.78%)	129	83.33%	79.01%	
$\geq$ 430ms		5(12.8%)	39			
<435ms		2(1.4%)	141	66.67%	85.80%	
$\geq$ 435ms		4(14.8%)	27			
<445ms		4(2.52%)	159	33.33%	95.68%	
$\geq$ 445ms		2(22.2%)	9			
<b>Combined cut-offs</b>				<b>96.77%</b>	<b>52.89%</b>	

Table 1. QTcF at 4 hours post first dose and week 3 in patients who developed severe QT/QTcF prolongation, and those who did not, using different QTcF cut-off values. The proposed cut-offs were significant at the 5% level at both time points. One patient in the prolongation group at 4 hours and three at week 3 in the no prolongation group had missing data so are not included in each analyses.

31 of 275 patients on the short regimen developed QT/QTcF  $\geq$ 500ms. No significant relationship between QT/QTcF  $\geq$ 500ms and QT/QTcF changes from baseline was identified. Absolute QT/QTcF values and development of QT/QTcF  $\geq$ 500ms was found to be significant ( $p < 0.05$ ) for the majority of cut-off levels explored at baseline, 4 hours, weeks 1-4 and 12.

Selection of the optimal values involved a trade-off between sensitivity and specificity; 425ms at 4 hours combined with 430ms at week 3 appeared most promising (Table 1). 5/30 patients were missed based on the 4 hours cut-off alone but all 5 patients would have been captured at week 3 and could then receive more frequent monitoring.

**Conclusions:** Our analysis suggests that using a combination of cut-offs with 425ms at 4 hours and 430ms at week 3 might permit a reduction in ECG monitoring frequency in 47% of patients on the short regimen. These results need further validation.

### OA-17-609-22 A study to determine the frequency of QT interval prolongation in people treated with bedaquiline for drug-resistant tuberculosis

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**Background:** Bedaquiline (BDQ) is a recent addition to the drug-resistant tuberculosis (DR-TB) armamentarium. In the licensing trials, excess mortality was observed in the BDQ treatment arm, which whilst not clearly related to QTc prolongation, resulted in a black-box warning of arrhythmias and sudden death associated with BDQ therapy. The aim of this study was to determine the incidence of QTc prolongation and cardiac events in patients receiving BDQ DR-TB therapy under routine conditions.

**Design/Methods:** This was a retrospective cohort study of routinely collected data at a DR-TB hospital in KwaZulu Natal, South Africa, from September 2017 to February 2019. Medical records, including ECG data, were transcribed using a digital collection tool. The QT interval was corrected for heart rate using the Fridericia formula (QTcF). The primary outcome, a prolonged QTcF, was defined as QTcF  $>$ 500ms, QTcF change  $>$ 60ms from baseline, or both.

**Results:** A consecutive sample of 419 medical records was reviewed. Patients had a median age of 36 years (29-44), 278/419 (66.4%) were male and 311/419 (74.2%)

were HIV positive. The mean QTcF was 406.0ms at baseline increasing to 433.3ms by week 12 and 437.5ms at week 24. 19/419 patients (4.5%) had a QTcF >500ms and 115/419 patients (27.5%) had a QTcF change >60ms. There were no arrhythmias or deaths attributable to arrhythmias. QTcF >500ms was more common in older patients (OR 3.61, 95% CI[0.81-18.0] for age >50 vs. age ≤30) and females compared to males (OR 2.36, 95% CI[0.84-6.72]). The odds of having a QTcF >500ms were lower in HIV positive patients (OR 0.48, 95% CI[0.17-1.41]). The QTcF declined after prolongation without clinical sequelae, whether drugs were interrupted (QTcF change -45.4ms, n=11) or not (QTcF change -26.8ms, n=10).

**Conclusions:** BDQ prolonged the QTcF but no arrhythmias or related deaths were observed. Management of QTcF prolongation with or without an interruption to BDQ therapy did not affect the outcome in patients.

### OA-17-610-22 Pretomanid added to bedaquiline and linezolid for patients with XDR-TB and MDR-TB treatment failure or intolerance: a comparison of prospective cohorts

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**Background:** In the Nix-TB study, 109 South African patients with XDR-TB or MDR-TB treatment failure/ intolerance receiving the oral 3-drug Nix regimen (bedaquiline, pretomanid and linezolid; BPaL) for 6-9 months achieved 90% favorable outcome at 6 months post-therapy, leading to the FDA approval of the BPaL regimen.

**Design/Methods:** To place this result in the context of contemporaneous regimens in use that included bedaquiline and linezolid, but not pretomanid, 6-month post end-of-treatment outcomes were compared between Nix-TB and 102 prospectively recruited South

African XDR-TB patients who received an ~18-month bedaquiline-based regimen (median of 8 drugs). A subset of the 102 patients received bedaquiline and linezolid (B-L combination; n=86) and a subgroup of these (n=75) served as individually matched controls in a pairwise comparison to determine differences in regimen efficacy.

**Results:** The 6-month post end-of-treatment favorable outcomes (%) were significantly better with BPaL than the B-L based combination regimen [89.9(98/109) versus 65.1(56/86); adjusted RR ratio 1.35; p<0.001] and in the matched pairwise analysis [89.3(67/75) versus 64.0(48/75); adjusted RR ratio 1.39; p=0.001], despite baseline significantly higher bacterial load and prior second-line drug exposure in the Nix-TB cohort. Time to culture conversion (p<0.00014), time to unfavorable outcome (p=0.0023), and time to death (p=0.027) were significantly better or lower with BPaL compared to the B-L-based combinations.

**Conclusions:** These analyses suggest that the Nix-TB regimen (and hence substitution of pretomanid and/or higher starting-dose linezolid) significantly improved outcomes in DR-TB patients with poor prognostic features.

### OA-17-611-22 Moxifloxacin pharmacokinetics and cardiac safety in children with multidrug-resistant tuberculosis

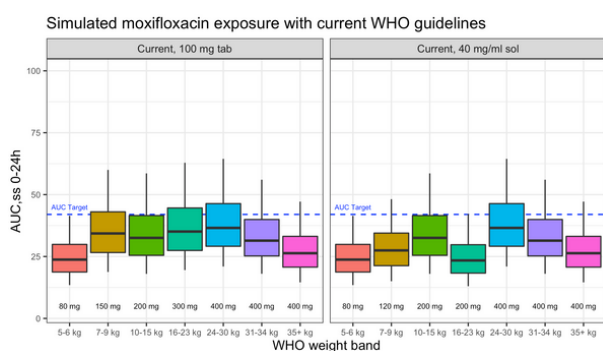
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**Background:** Moxifloxacin is a high-priority drug for multidrug-resistant tuberculosis (MDR-TB) treatment. Moxifloxacin use in children is typically limited to older children due to formulation availability and the lack of published pediatric pharmacokinetic or safety data. We characterize moxifloxacin population pharmacokinetics and QT-interval prolongation in children treated for MDR-TB and evaluate optimal dosing.

**Design/Methods:** Moxifloxacin plasma concentrations were measured in children 0-17 years routinely treated for MDR-TB in two South African observational pharmacokinetic studies. Moxifloxacin doses were ~10mg/kg once daily. Electrocardiograms were done during pharmacokinetic sampling. QT-intervals were corrected by Frederica formula (QTcF). Moxifloxacin population pharmacokinetics, including child factors influencing drug exposure, and the exposure-response relationship with QTcF were characterized. Dosing simulations were performed to evaluate predicted child exposures compared to adults.

**Results:** Eighty-five children were included (median [range] age of 4.6 [0.8-15] years). A two-compartment distribution model described the pharmacokinetic data well. Estimated clearance was 7.33 L/h in a 16 kg child. HIV-positive, malnourished, and young children had lower drug exposures. Five children had a QTcF >450ms. The highest observed QTcF values were 482 and 491; those children were also taking clofazimine. The median (range) change in QTcF from baseline (dQTc) was 14 (0-52) ms. Moxifloxacin significantly increased the QTcF by 2.50 ms per mg/L, similar to adults. Of the 11 children with dQTc >30 ms, 7 were taking clofazimine.

Model-based simulations predicted that most children in all weight bands would not reach the adult AUC target of 42 mg\*h/L with 10-15 mg/kg dosing as recommended by the World Health Organization. Higher doses are likely needed in children, especially those <15 kg.



[Figure]

**Conclusions:** Moxifloxacin doses above 10-15 mg/kg are likely required in young children to match adult exposures but would require further safety assessment. Further investigation of age and formulation effects is required. Moxifloxacin increased the QTcF similarly to adults.

## OA-18 (Im)possible mission: TB care in low-resourced settings

### OA-18-612-22 Enabling MPs to support and take ownership of India's TB program

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**Background and challenges to implementation:** India's national TB elimination program (NTEP) aims to eliminate TB by 2025. The strategies outlined in its National Strategic Plan (2017-2025) integrate technology and innovation to reach ambitious targets, relying heavily on its expansive structure and workforce. Yet, in order to succeed the program needed localized review and troubleshooting mechanisms, with political will and ownership driving them forward.

**Intervention or response:** Given their authority and mandate, Members of Parliament (MPs) had to be more involved in the program and engender success. In 2018-2019, Global Health Strategies worked with MPs to enable them to play a supportive supervisory role in districts tied to their constituencies and provide them with tools to do so. GHS developed a dashboard (in consultation with the NTEP and WHO) which includes relevant indicators, to assist MPs in understanding the status and challenges of the TB program in their districts. They were therefore able to use the dashboard, and work with their District TB Officers (DTOs) to review progress and support them in addressing challenges they face.

**Results/Impact:** Till date, 10 MPs have conducted reviews with DTOs, using the dashboard as a reference point, and initiating supportive corrective actions to address challenges, such as establishing district-level taskforces to improve inter-departmental coordination, issuing letters to private sector healthcare providers reminding them about mandatory notification policy and writing to the NTEP to improve human resource capacity at the district level.

**Conclusions:** This pilot initiative showed that MPs, when provided with the right tools and information, are well placed to support the NTEP and catalyze quick corrective action to address challenges in a local context. In a COVID-19 wrought world, political involvement and ownership of TB programs will be necessary to ensure uninterrupted operations.

### OA-18-613-22 99DOTS for tuberculosis treatment supervision in Uganda: adherence rates and acceptability

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**Background:** 99DOTS is a low-cost digital adherence technology with potential to improve tuberculosis (TB) treatment adherence and completion, which is currently 72% in Uganda. Providers receive real-time data on medication adherence when patients make a toll-free call daily to confirm dosing, facilitating monitoring and targeted resource allocation. We aimed to evaluate treatment adherence, benefits and challenges of using 99DOTS.

**Design/Methods:** We implemented 99DOTS at 18 health facilities in 15 districts of Uganda, training three facilities per month January-June 2019. Demographics and medication adherence for all patients enrolled on 99DOTS in 2019 were extracted from the 99DOTS system. Total patient volume was collected from TB treatment registers. Surveys were conducted with a random sample of patients and providers to assess acceptability of implementing 99DOTS.

**Results:** Of the 3738 patients initiating TB treatment at health facilities using 99DOTS between January 1-December 31, 2019, 1528 (41%) were enrolled on 99DOTS. The most common reason (nearly 50%) for non-enrollment was lack of access to a phone. Of the expected 229487 doses of anti-TB drugs taken by patients enrolled on 99DOTS, 123063 (53.6%) were confirmed by patient phone call and 211055 (92%) were marked as taken after incorporating doses manually-added by providers. Adherence was >80%, >90% and 100% in 1320 (86.4%), 1160 (75.9%) and 672 (44.0%) patients, respectively (Table1). Of 115 patients surveyed, 99(86%) reported reduced clinic visits, 114(99%) reported increased connection to their healthcare workers, and 114(99%) were comfortable using 99DOTS from anywhere.

However, 56 (49%) patients reported occasional difficulty in making calls to 99DOTS due to low battery or poor network. Whereas 21/22 (95%) providers reported reduced workload, 18/22(82%) reported occasional difficulty in accessing the 99DOTS dashboard due to software malfunctions.

**Conclusions:** Patients using 99DOTS achieved high levels of adherence. Despite challenges of phone availability, poor network and software malfunctions, patients and providers found the technology acceptable and convenient.

Variable	Female, n(%)	Male, n(%)	All patients, n(%)
Total number patients enrolled on 99DOTS	570 (37.3)	958 (62.7)	1528
Total number patients still on treatment using 99DOTS	107 (34.7)	201 (65.3)	308
Total expected doses	85491	143996	229487
Total doses due to direct calls by patients	46954 (54.9)	76109 (52.9)	123063 (53.6)
Total doses recorded as taken (Direct calls and Manual doses)	79339 (92.8)	131716 (91.5)	211055 (92.0)
Number of Patients with recorded doses taken > 50%	549 (96.3)	903 (94.3)	1452 (95.0)
Number of Patients with recorded doses taken > 80%	496 (87.0)	824 (86.0)	1320 (86.4)
Number of Patients with recorded doses taken > 90%	440 (77.2)	720 (75.2)	1160 (75.9)
Number of Patients with recorded doses taken 100%	258 (45.3)	414 (43.2)	672 (44.0)

[Table.]

### OA-18-614-22 Determinants of delayed diagnosis and treatment of tuberculosis in high-burden countries: a mixed-methods systematic review and meta-analysis

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**Background:** Delayed diagnosis and treatment are detrimental to tuberculosis (TB) prognosis and sustain TB transmission in the community, especially in high TB burden countries. Our objective was to elucidate the determinants and duration of delayed diagnosis and treatment of pulmonary TB in high TB burden countries.

**Design/Methods:** We conducted a systematic review and meta-analysis of quantitative and qualitative studies by searching four databases for literature published between 2008 and 2018 following PRISMA guidelines. For quantitative studies, we performed narrative synthesis of the covariates that were significantly associated with patient, health system, treatment, and total delays. The pooled median duration of delay and effect sizes of covariates were estimated using random-effects meta-analyses. We identified key qualitative themes using thematic analysis.

**Results:** We included 124 articles from 14 low-and lower-middle-income countries (LIC and LMIC) and five upper-middle-income countries (UMIC) in this review.

The pooled median duration of patient, health system, and treatment delay were 28 days (95% CI 20–30), 11.5 days (95% CI 3.9–24.7), and six days (95% CI 1–28.4), respectively. We found that the duration of delays was consistently shorter among UMIC compared to LIC and LMIC. There was consistent evidence that being female and rural residence was associated with longer patient delay. Furthermore, patient delay was also associated with poor TB knowledge, long chains of care-seeking through private/multiple providers, perceived stigma, financial insecurities, and poor access to healthcare. Health system and treatment delay were mediated by organizational and policy factors such as the lack of resources and complex administrative procedures at the health facilities. We identified data gaps in 11 high burden countries.

**Conclusions:** The gaps identified at different socio-ecological levels could be addressed through tailored approaches, education, and at a higher level, through health system strengthening and provision of universal health coverage to reduce delays and improve access to TB diagnosis and care.

#### **OA-18-615-22 The effect of depression, anxiety, and other risk factors on adherence to anti-tuberculosis treatment in the Philippines**

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**Background and challenges to implementation:** Limited data exist on the prevalence and effects of depression in Filipinos with TB on adherence to treatment. This study investigates reasons for non-adherence among Filipinos enrolled in public TB-DOTS centers and the St-ATT cohort (ISRCTN16347615).

**Intervention or response:** Adult participants were enrolled in public facilities in Metro Manila, Cebu, and Negros Occidental from June 2019 to January 2020 within 5 days of starting the treatment. Depression (HADS $\geq$ 8) and Anxiety symptoms (HADS $\geq$ 8) were assessed using The Hospital Anxiety and Depression Scale, Social-family support using the Multidimensional scale of perceived social support, Stigma using TB-related stigma scale, and adherence using the Morisky Medication Adherence Scale (score $<$ 6). Multivariable logistic regression was used to model risk factors (depression and anxiety at enrolment) on the outcome of non-adherence, assessed after one month of initiating treatment. A forward-stepwise approach was used to select a final multivariable model with inclusion based on global tests of significance with  $p<0.05$ .

**Results/Impact:** In 282 persons, the prevalence of depression and anxiety at enrolment was 8.9% and 33% respectively. Of 236 with adherence data at the first-month follow-up, mean age 43.3 years [range: 18-87], 75% male, the prevalence of depression and anxiety at enrolment was 7.2% and 32.2% and 29.2% were non-adherent. The proportion nonadherent in depressed vs. non-depressed was 58.8% vs. 26.9%  $p=0.005$  and proportion nonadherent in anxious vs. non-anxious was 39.5% vs. 24.4%,  $p=0.017$ ). After adjustment for age, sex, and region, depression and anxiety were associated with nonadherence (OR=2.56 (95% CI 0.84–8.11)) and (OR= 2.00 (95% CI 1.06–3.77)) respectively. Social and family support and stigma were not associated.

**Conclusions:** Depression and anxiety symptoms are common among Filipinos with TB and independently associated with nonadherence behavior. Social and psychological interventions may improve medication compliance levels. Further analyses of repeated measurements throughout treatment are planned.

#### **OA-18-616-22 Impact of HIV “test-and-treat” policy on the incidence of Tuberculosis in HIV populations in East-Central Uganda**

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**Background:** Early antiretroviral therapy (ART) is known to reduce the risk of Tuberculosis (TB) among people living with HIV (PLHIV). In Uganda, eligibility for ART initiation changed in 2009 from CD4  $\leq$ 350 to  $\leq$ 500 cells/ $\mu$ L. In 2016, Uganda adopted the test-and-treat ART initiation policy. This policy’s impact on TB incidence among PLHIV in Uganda has not been studied. USAID’s Regional Health Integration to Enhance Services in East Central Uganda (RHITES-EC) conducted this study to determine TB incidence before and after this policy’s adoption.

**Design/Methods:** This retrospective study collected and analyzed data for individuals ( $\geq$ 15 years) receiving ART at Jinja Regional Referral Hospital between January 1, 2005 and December 31, 2018, including TB status and year of initiating ART. Client data were categorized into three eras according to date of ART initiation: era I (before 2009), era II (2009-2015), and era III (2016-2018, during test-and-treat). Cumulative TB incidence was calculated as the proportion of total new TB cases out of the total patients starting ART in each era. Odds ratios were determined for association between treatment era and TB incidence.

**Results:** Of the 3,941 clients, 383 (9.7%) participants developed TB while receiving ART. The cumulative incidence of TB was: 16.1% in era I, 9.5% in era II and 6.3% in era III. The odds of TB during era I and era II were 2.5 times (95% CI; 1.6-3.9,  $p<0.0001$ ) and 1.6 times (95% CI; 1.02-2.24,  $p=0.04$ ) the odds of TB in era III.



**Conclusions:** Incidence of TB progressively reduced with each era and was lowest during the era of the test-and-treat policy, which shows that the policy had a positive impact on reducing the incidence of TB among PLHIV in Uganda.

We thus recommend the widespread adoption of strategies to improve timely initiation of all newly diagnosed PLHIV on ART.

### **OA-18-617-22 Utility and benefits of Tuberculosis Molecular Bacterial Load Assay (TB-MBLA) to monitor TB therapy in a resource limited high burden setting**

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**Background:** Rapid and accurate tests are needed for monitoring tuberculosis (TB) therapy. The gold standard culture is very slow while microscopy and Xpert MTB/RIF tests fail to differentiate viable from dead bacilli essential for monitoring. We explored the utility and benefits of novel TB-MBLA for monitoring TB therapy in routine settings.

**Design/Methods:** Therapy naïve, Xpert MTB/RIF positive patients were recruited at 4 routine healthcare facilities in Mbeya, Tanzania for 6 months of standard anti-TB therapy. Treatment response was assessed at week 2, month 2, 5 and 6 of follow-up using TB-MBLA, standard smear microscopy, culture, and clinical sign inspection. Attending clinicians were trained on interpretation of TB-MBLA results and the NIMR-Mbeya Medical Research Centre, TB-laboratory was used as a hub for culture and TB-MBLA tests.

**Results:** A total of 46 patients aged 37 (18-65) years, 60.9% (28/46) male and 39.1% (18/46) HIV positive were analysed. At baseline, all patients were TB-MBLA positive with mean ( $\pm$ SD) bacterial load  $5.48 \pm 1.3 \log_{10} \text{eCFU/mL}$ , declining to 60.9% and 8.6% positivity corresponding to  $3.42 \pm 0.7$  and  $3.51 \pm 0.62 \log_{10} \text{eCFU/mL}$  bacillary load at month 2 and 6 of treatment respectively. In contrast, positivity of ZN microscopy and culture were 84.8%, 8.6% and 0%, and 93.5%, 28.3% and 2.2% at baseline, month 2 and 6, respectively. Except cough which resolved in parallel with bacillary load clearance, most clinical signs resolved earlier in treatment when patient bacillary load was still substantially high. Turn-around-time for TB-MBLA results was 24h compared to 14.83 (4.33-42) days for MGIT culture. Unlike TB-MBLA, >40% of MGIT results were indeterminate due contamination at 5 and 6 months of treatment. 100% of participating healthcare practitioners indicated they would implement TB-MBLA in their routine care.

**Conclusions:** TB-MBLA provides rapid and accurate results in time to inform clinical management of TB patients and can be applied in high burden settings.

### **OA-18-618-22 Using TB care process mapping to improve treatment retention and treatment success rate in low-income settings: experience from central Uganda**

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**Background and challenges to implementation:** Based on World Health Organization's 2019 Global Tuberculosis (TB) Report, TB treatment success rate (TSR) for newly diagnosed TB was 85% in 2017, below the 95% global target. Between 2002 and 2016, Uganda's TSR stagnated between 70% -75%, far below the 85% national target. TB patient retention is a contributor to TSR; so, improving retention is important for TSR. An assessment by USAID Defeat TB project in April 2019 showed that 83% (25/30) of high volume TB treatment facilities had not attained the 85% national target for patient retention over the previous 3 months. Of the 17% achieving the target, non was consistent in the preceding 3 months. The project there after supported health facility teams to improve patient retention.

**Intervention or response:** USAID Defeat TB project oriented 30 health facility teams with low TSR on process analysis and quality improvement (QI) tools. Through on site coaching, teams were guided to assess performance and conduct root cause analysis to determine the main reasons for low TB treatment retention and completion. The teams identified root causes, and through regular coaching by improvement coaches, teams implemented changes targeting each root cause while measuring the effect of the changes. Through implementing changes, gaps in TB care were continuously addressed thus improving performance.

**Results/Impact:** The proportion of health facilities meeting the retention on treatment target (85%) increased from 17% in the pre-intervention period to 80% by December 2019. The TSR for all forms of TB improved from 78% to 83 in the October to December 2018 quarter and October to December 2019 quarter respectively.

**Conclusions:** TB care process analysis and implementation of corrective changes at treatment facilities improves TB patients' retention and treatment success rate. The results of this intervention provide lessons that can be scaled up for countries aiming to improve TB treatment success rate.

## OA-19 Histories of success: improving TB and latent TB infection care

### OA-19-619-22 Utility of stool CBNAAT in the diagnosis of pediatric pulmonary tuberculosis in India

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**Background:** Tuberculosis in children accounts for 11% of the cases worldwide and 6% of the cases in India. Gastric aspirate (GA) and induced sputum samples are used for microbiological confirmation but are difficult to obtain. We aimed to study diagnostic utility of Stool Cartridge Based Nucleic Acid Amplification Test (CBNAAT) in comparison to GA CBNAAT and culture, among the suspected cases of tuberculosis in children.

**Design/Methods:** 75 children aged 6 months to 12 years suspected to have pulmonary tuberculosis on the basis of national tuberculosis guidelines, presenting to a tertiary care hospital in New Delhi, India were enrolled. Detailed clinical evaluation, chest radiograph, Mantoux and other relevant investigations were done. Gastric aspirate and stool samples were obtained. Cultures by Mycobacterial Growth Indicator Tube (MGIT) and CBNAAT were done on both gastric aspirate and stool.

**Results:** The mean age of children enrolled in our study was  $6.74 \pm 3.57$  years. Of the 75 children enrolled, 28 were started on antitubercular therapy, 12 of whom were microbiologically confirmed and 16 were started on the basis of clinical diagnosis. Overall, 11 (14.6%), 11(14.6%), 10 (13.3%) and 4(5.3%) were positive by GA MGIT, GA CBNAAT, Stool CBNAAT and Stool MGIT, respectively. Gastric aspirate CBNAAT and Stool CBNAAT were found to have near perfect agreement (Cohen's kappa 0.834). Stool CBNAAT had sensitivity and specificity of 73% and 97% as compared to culture (GA MGIT).

CBNAAT	GA CBNAAT			Weighted Kappa		
	Positive	Negative	Total	K	p value	
Stool CBNAAT	Positive	9 (12.0%)	1 (1.3%)	10 (13.3%)	0.834	<0.001
	Negative	2 (2.7%)	63 (84.0%)	65 (86.7%)		
	Total	11 (14.7%)	64 (85.3%)	75 (100.0%)		

[Table.]

**Conclusions:** Stool CBNAAT may be used for bacteriological confirmation of pediatric pulmonary tuberculosis instead of gastric aspirate. This would be helpful

in endemic countries where there is a dearth of trained staff, especially in the periphery, to obtain gastric aspirate samples. Discomfort to the child is avoided.

### OA-19-620-22 Improving TB treatment outcomes: the role of the Quality Improvement approach: a case of Nairobi City County, Kenya

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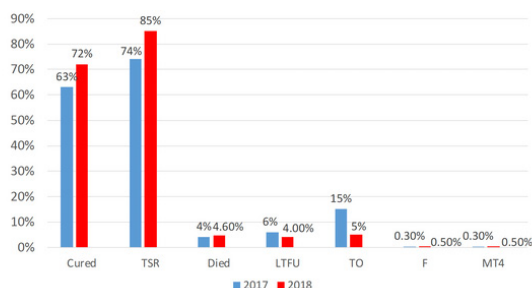
**Background and challenges to implementation:** Quality Tuberculosis (TB) care is a major focus towards ending TB. While there has been growing recognition of the benefits of adopting a Quality Improvement (QI) approach, implementation in TB programming has been limited. Following a data review, Nairobi County, the highest burden county contributing approximately 15% of Kenya's TB cases, had suboptimal treatment outcomes in 2017 compared to national annual targets.

**Intervention or response:** Through the USAID-funded TBARC II project, Nairobi County, was supported to implement a QI approach towards improving TB treatment outcomes. TBARC II supported a QI training for TB Coordinators and health care workers managing 236 TB clinics. These coordinators (improvement coaches) established facility Work Improvement teams, to identify and quantify gaps in systems and processes, test small changes and new ideas in order to improve TB Treatment outcomes and evaluating data to monitor improvement. Through the Plan-Do-Study-Act Model of Improvement, TB Support supervision was enhanced, peer to peer cross learning was encouraged, and TB data quality evaluated through monthly data review meetings. Chi-squares were used to test for differences in treatment outcomes before and after the interventions.

**Results/Impact:** Compared to the 2017 cohort, TB treatment outcomes for the 2018 drug-sensitive TB cohort compared as follows; Treatment Success rate increased from 74% (9433/12803) to 85% (11584/13494) (P value <0.001), Cure rate increased from 63% (4052/6634) to 72% (4974/7009) (P value <0.001) loss to follow-up dropped from 6% (775/12803) to 4% (552/13494) (P value <0.001) and transfer outs dropped from 15% (2002/12803) to 4% (626/13494) (P value <0.001).

These results demonstrated significant improvement across all TB outcomes, impacting overall county and country treatment outcomes

**Conclusions:** QI models offer a sustainable team-driven approach towards improving TB indicators by leveraging on already existing systems. The approach can be scaled up country-wide to improve the country's treatment outcomes.



[Figure. Nairobi county DSTB treatment outcomes (2017 - 2018)]

**OA-19-622-22 Use of intravenous isoniazid and ethambutol administration in patients with new sputum positive drug-susceptible pulmonary tuberculosis with tuberculous meningoencephalitis and HIV co-infection**

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**Background:** The aim of our study was to investigate the use of intravenously isoniazid and ethambutol administration in patients with new sputum positive drug-susceptible pulmonary tuberculosis (TB) with tuberculous meningoencephalitis (TM) and human immunodeficiency virus (HIV) co-infection in the intensive phase of treatment.

**Design/Methods:** This prospective, randomized, comparative, open, two parallel study on the comparative evaluation of effectiveness and tolerability of the treatment with the use of intravenous anti-TB drugs (isoniazid and ethambutol) and standard therapy based on orally administered anti-TB drugs in patients with new smear-positive drug-susceptible TB with TM and HIV co-infection in the intensive phase of treatment. Fifty-four patients with TB/TM and HIV co-infection were enrolled in this study.

Group 1 included 23 patients treated with ethambutol and isoniazid intravenously, while rifampicin and pyrazinamide were prescribed orally. Group 2 consisted of 31 patients treated with the first-line anti-TB drugs orally. Concentrations of isoniazid and ethambutol in blood serum were detected using a chromatographic method.

**Results:** A significant improvement in clinical symptoms and X-ray signs in patients treated intravenously with isoniazid and ethambutol was observed compared with group 2. Sputum Mycobacterium tuberculosis positivity was observed during the second month of treatment in

25.0 % of patients from group 1 and 76.1% of patients from the control group ( $p < 0.01$ ). In addition, 9 (39.1%) patients died up to six months when isoniazid and ethambutol were prescribed intravenously compared with 22 (70.9%) in group 2 ( $p = 0.02$ ).

**Conclusions:** In TB/TM with HIV, intravenously isoniazid and ethambutol treatment was more effective than oral isoniazid and ethambutol treatment at 2 months of intensive treatment in sputum conversion as well as in clinical improvement, accompanied by significantly higher mean serum concentrations. In addition, the mortality rate was lower in intravenously isoniazid and ethambutol treatment than oral.

**OA-19-623-22 When facility-based detection is not enough: Increasing tuberculosis case detection through a social and behavior change strategy in Nigeria**

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**Background and challenges to implementation:** The World Health Organization considers Nigeria a high burden country for TB. Despite high TB incidence, Nigeria has one of the lowest case detection rates among high TB burden countries, with just 24 percent of estimated cases notified in 2018. Low community awareness and/or high misinformation about TB is a barrier to increasing care-seeking behavior and detection.

**Intervention or response:** USAID's SHOPS Plus Nigeria program increases access to TB services in the private sector by establishing networks of private providers (clinicians, medicine vendors, community pharmacists, and labs) to detect, diagnose, and treat TB. To drive patients into these networked facilities SHOPS Plus designed a community-led social and behavior change (SBC) strategy where healthcare providers and community leaders partner to educate and mobilize community members to seek care for their TB symptoms.

SHOPS Plus uses GIS data of de-identified patients on treatment to select and target outreach sites to screen for presumptive cases and increase access to information on TB and where to seek treatment. SHOPS Plus also trains and equips community volunteers providing them aides and SBC materials for educating their communities about TB.

**Results/Impact:** Since June 2019 SHOPS Plus has used GIS data to target TB high burden communities for outreach activities. Providers have educated and screened 27,504 individuals in Lagos and Kano States, identifying 546 TB cases, 11 percent of all cases identified by the private sector networks during that period.

**Conclusions:** To increase TB case detection in Nigeria, using GIS data of diagnosed de-identified patients to locate high burden areas for community education and TB screening can provide significant increase in case finding. In addition, as TB awareness increases and community identification and referral increase, individuals will be more likely to seek healthcare for screening, testing, and treatment for TB.

### OA-19-624-22 Treatment uptake in people with tuberculosis detected by active case finding in Ca Mau Province, Vietnam

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**Background:** Community based active case finding (ACF) is one promising strategy for accelerating reductions in TB incidence in high burden regions. The effectiveness of community based is dependent on a robust diagnostic and treatment cascade; a high proportion of individuals with a positive screening test must attend further diagnostic testing, initiate and complete TB therapy for ACF to be successful.

**Design/Methods:** All adults living in 60 villages were screened for active TB annually over 4 years and all adults in a further 60 villages were screened once. All participants who were able to spontaneously expectorate sputum submitted one specimen, which was tested using Xpert MTB/RIF (Cepheid). Xpert MTB positive participants were invited to attend the provincial TB center for chest x-ray and clinical assessment and to provide a further two sputum specimens for smear and culture. The decision about whether to recommend treatment for tuberculosis was made by the attending clinician. We estimated the proportion of Xpert MTB positive individuals who completed clinical evaluation and treatment.

**Results:** Of the 489 participants with a positive Xpert MTB/RIF test, 31 (6.4%) did not complete their clinical assessment, including 22 who did not attend at all and a further nine who did attend but did not complete the assessment. Among the 458 who did complete the clinical assessment, the clinician recommended treatment for TB in 420 participants (91.7%). Among these, two (0.4%) patients died before completing treatment and 20 (4.1%) did not complete treatment.

**Conclusions:** Overall, a high proportion of people diagnosed with TB during community-wide screening commenced and completed treatment for TB. Failure to attend for further assessment was the major reason for non-commencement of treatment.

### OA-19-625-22 Analysis of large patient-level dataset to predict outcome of treatment for patients with drug-sensitive and drug-resistant tuberculosis

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**Background:** Generally the success rate for drug-sensitive (DS) TB treatment is high, while it is significantly lower for multidrug-resistant (MDR), and even lower for extensively drug-resistant (XDR), TB cases. Establishing factors that are associated with different treatment outcomes may help optimize treatment for the most problematic patients.

**Design/Methods:** We constructed correlation matrices to explore the relationship among demographic, clinical, genomic, and radiological features available for patients from the NIAID TB Portals dataset. Then we applied various machine learning techniques (Logistic Regression, Random Forest, etc.) to correctly predict the known treatment outcome (either „cured“ or „died“) based on all above mentioned features. These models were applied to three distinct patient cohorts, grouped by drug resistance level (DS, MDR, and XDR). The modeling performance was evaluated with Area Under the Receiver Operating Characteristics (AUROC) and Precision-Recall Curve on a testing set that consisted of 30% of all patients.

**Results:** We included 1,164 patient cases in our analysis and grouped them according to drug resistance level: DS (n = 200), MDR (n = 642), and XDR (n = 322). The features most associated with unsuccessful treatment in all three groups were BMI, parameters from culture and microscopy tests, overall percentage of abnormal lung volume, and employment status. Additional variables were associated differently within each group. The relationship directions between features and the treatment outcome were provided by logistic regression coefficient and correlation coefficient. All AUROCs were higher than 0.7. A sensitivity analysis with post-treatment drug regimens further increased the predictive ability of the models.

**Conclusions:** Application of correlation analysis and predictive models to the large unique dataset of tuberculosis patients (<https://data.tbportals.niaid.nih.gov/>) demonstrated the power of data mining for translational medicine. Clinical, socioeconomic, radiological and genomic features, identified to be predictive of treatment outcomes, may help to quickly identify TB patients requiring additional attention.

## OA-21 Finding missing people with TB: targeted approaches

### OA-21-626-22 TB screening and treatment by neo-literate community volunteers among tribal populations in insurgency hit 'Swabhiman Anchal' (cut-off-area) saved life and livelihood in Malkangiri district, Odisha

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**Background and challenges to implementation:** Tuberculosis is the biggest killer among infectious diseases, claiming more than 4000 lives each day. An estimated 10 million people developed TB in 2018, and nearly half a million people developed drug resistant TB. In spite of complete geographic coverage of NTP in India, many TB suspects remain undiagnosed among vulnerable populations in difficult & hard to reach areas.

Sandwiched between a large reservoir on one side and daunting hills on the other side, the 'Swabhiman Anchal', dominated by a strong 40000 ethnic tribal populations is debarred from availing basic amenities/livelihood including healthcare facilities of the government because of intense insurgency activities by the outlawed CPI-Maoist; a Left-Wing Extremist Organization present in the area. Accessing to reach the villages takes around ten hours by boat (to cross the reservoir) and then walk/ride mules and horses for hours. TB care becomes a nightmare and most of the people remain undiagnosed/untreated and die.

**Intervention or response:** Inspired by series of special developmental activities initiated by the district administration to downplay insurgency in the Swabhiman Anchal, NTP-Malkangiri took up TB screening and treatment activities in the area. Local Community Volunteers (born, raised, living in the area) including the Accredited Social Health Activists, Angan Wadi Workers (ICDS) and the healthcare workers were involved and engaged in TB screening, diagnosis, treatment and follow-up activities.

Interested and willing semi-literate youths were trained in sputum microscopy to fix sputum slides. Every Village Panchayat with around 5000 population base got a sputum collection centre (Sputum House) and trained community volunteers designated there collected and transported sputum samples to the nearest established slide fixing centre which are then sent to the mainland DMCs for examination thrice weekly. People were informed and encouraged to give sputum at weekly/fort-

nightly health camps organised on local market days. Sputum results were made available to the treatment centres within 3–7 days.

Diagnosed patients were initiated treatment immediately after the results received by the centre and trained neo-literate/semi-literate local Treatment Supporters were engaged for treatment activity as per NTP's daily regimen schedule. Pictorial referral slips and graphical treatment cards, as developed locally, were used for monitoring treatment of patients. Sub district level NTP supervisors provided regular technical and logistical support to the ground team and registered every patient in to the NIKSHAY portal. CVs were paid as per NTP norms for referral/SCT and treatment activities.

**Results/Impact:** Around 25,000 (of 40000) populations in 160(of 251) villages were reached out with TB messages/services by 160(of 250) trained community volunteers thru 84 health check up/sputum collection camps and regular visits during 2019. 682 sputum samples examined of 538 sputum referred & 189 collected/transported with 82 TB patients diagnosed. TB awareness encouraged around 10% people to report at the Sputum Houses on their own. This intervention added 14% sputum examination (682/4750) and 7% notification (82/1220) in to the district fold. Treatment compliance/adherence was 100% with 50% diagnosed cases initiated treatment on the same day, 30% in 2-5 days and the rest within a week.

Population	No. of villages	No. of Neo-literate CVs engaged	No. of health camps organised	No. of sputum referred	Sputum collected and transported	Total sputum tested	Patients diagnosed	Diagnosed TB patients put on DOTS
40000	251	250	84	538	189	682	82	82

[Table 1. TB screening and treatment status of Swabhiman Anchal by neo-literate Community Volunteers in Malkangiri district, Odisha during 2019]

**Conclusions:** Concerted efforts of TB-screening and treatment saved 82 lives in the cut-off area where insurgent Maoists had a free run. Reaching out with tuberculosis services among the hard to reach vulnerable ethnic groups on a sustained approach by engaging the community themselves and by adapting out of box strategies will bring a significant impact on the disease prevalence and mortality among such community. Stronger political and administrative commitment in NTP is required for diagnosis and standard of care for such deprived community.

### OA-21-627-22 Investigating the feasibility of universal screenings and institutional treatment support of the homeless population through a mobile digital x-ray and CBNAAT algorithm in India

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**Background and challenges to implementation:** To investigate and demonstrate the feasibility and importance of universal mass screenings and institutional treatment using a mobile digital x ray and CBNAAT algorithm for the homeless population in India.

**Intervention or response:** This pilot study conducted in Delhi, India universally screened a large homeless population on the eastern river bank of the Yamuna using a mobile digital x ray and a symptom checklist. Symptomatic patients were referred to a govt hospital to see a doctor and have a CBNAAT and AFB sputum test. Patients diagnosed with TB or any other serious disease were offered institutional care at a recovery shelter very close (>2km) to the site of the screening.

**Results/Impact:** A total of approximately 2500 persons were approached, 1249 (50%) patients were screened and 369(29.5%) needed further investigation. There were 69 (5.5%) CBNAAT positive and 58 (4.6%) AFB positive diagnoses with a higher proportion of drug resistant TB, EPTB and previous TB diagnosis as compared to housed populations. From all confirmed cases 48 (69.5%) opted for institutional care with 5 (7.2%) documented deaths within 1 week of diagnosis.

**Conclusions:** There is a huge burden of untreated TB amongst the homeless population of Delhi. Universal Screening using a mobile digital x ray and CBNAAT algorithm is a viable algorithm and preferable compared to a AFB. A mix of both institutional as well as non-institutional treatment support mechanism must be offered to the homeless population to ensure treatment completion. As the Indian government makes a bold commitment to the new TB Elimination Program it must create specialised case finding and treatment services for key affected populations like the homeless.

### OA-21-628-22 Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in Ukraine

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**Background and challenges to implementation:** Multidrug-resistant tuberculosis (MDR-TB) poses a serious threat to tuberculosis (TB) control in Ukraine and worldwide. MDR-TB treatment outcomes in Ukraine are suboptimal: analysis of the 2016 MDR-TB cohort shows that 17% of patients were lost to follow-up (LTFU), which is substantially higher than the WHO recommended target of 5%. The current study investigated factors associated with LTFU among new MDR-TB cases starting treatment in 5 regions of Ukraine with the highest LTFU rates.

**Intervention or response:** This was a retrospective cohort study of all newly diagnosed MDR-TB cases reported to the National electronic TB database (e-TB-Manager) from January 1, 2016, to December 31, 2016 from 5 regions with the highest LTFU rates (Chernihiv, Poltava, Zakarpattia, Zaporizhia, Kyiv). Univariate and multivariate logistic regression analysis was carried out to identify risk factors independently associated with LTFU among MDR-TB.

**Results/Impact:** In total 1287 patients were included in the analysis, of these, 212 (16.5%) were LTFU, of these 96 patients (45%) were LTFU in the inpatient facilities. Following a multiple multivariate logistic regression analysis, risk factors independently associated with LTFU were: history of prior incarceration (OR 2.42 (95%CI 1.41-2.20), p=0.001) and homelessness (OR 1.75 (95%CI 1.04-2.94), p=0.035). The age bracket 55-64 years (OR 0.40 (0.17-0.93), p=0.033) was the only protective factor against LTFU. Reentry after LTFU and treatment failure appeared as risk factors.

**Conclusions:** LTFU is high among MDR-TB patients in Ukraine and poses a significant public health risk. A multi-pronged approach to address the various patient- and treatment-related characteristics associated with LTFU as well as targeted interventions aimed at increasing treatment adherence may substantially reduce the risk. Proposed interventions could include improving education, encouragement, psychosocial support, elimination of tuberculosis-related patient costs, strengthening social support networks, earlier enrolment patients in support programmes and expanding people-centred models of TB-care.

### OA-21-629-22 Promoting a community-led, multi-sectoral and collaborative response to tuberculosis: learnings from India

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**Background and challenges to implementation:** Despite TB being a socio-economic disease, the TB response has remained largely biomedical, with minimal involvement of communities and other actors. This has adversely impacted public understanding of TB, and limited community participation in efforts to support people with TB.

**Intervention or response:** Between 2016 and 2019, the USAID-supported Call to Action project was implemented to engage previously unengaged stakeholders and broaden the conversation. In six priority states, TB survivors, industry leaders, elected representatives, media, celebrities, etc. were sensitised on their potential role through a combination of workshops, meetings and one-to-one follow-ups. Opportunities were created for stakeholders to interact with each other – TB survivors met with elected representatives to strengthen their understanding of how TB affects a person's life; industry leaders with officials to implement the Employer Led Model (ELM).

**Results/Impact:** Over 300 TB survivors were trained as TB Champions and seven survivor-led networks formed. TB Champions touched the lives of over 12,000 people with TB and made over 150,000 people aware of TB. 100 companies, most employers of vulnerable populations, signed Letters of Intent to implement ELM. Elected representatives launched TB-free campaigns in constituencies. Celebrity ambassadors featured in campaigns to reduce stigma. State governments brought together representatives from departments beyond health for intersectoral responses. Trained journalists wrote over 100 stories on neglected dimensions of TB. All of this resulted in the TB programme's recognition of the unique role of each stakeholder.

**Conclusions:** A multi-sectoral, community-led approach is essential to trigger collective action and translate global commitments to end TB into action. Increased investment in strategic advocacy, communications and engagement of communities can result in more resources, greater visibility and more attention for TB. This intervention demonstrated and documented innovative processes of engaging stakeholders, with the potential for scale-up and expansion across India, and globally.

### OA-21-630-22 Towards a Nairobi TB free city: engaging city authorities towards the elimination of TB. The case of the Nairobi City County government

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**Background and challenges to implementation:** Kenya is among 14 countries with the highest burden of tuberculosis (TB). Tuberculosis is the fourth leading cause of mortality in the country. Routine data indicates that Kenya's capital, Nairobi City County (NCC), has the highest TB burden; contributing 15% and 25% of the country's TB cases and mortality respectively. The 2016 prevalence survey indicated that 40% of TB cases were not diagnosed.

**Intervention or response:** Through the USAID funded TB ARC II project, the Center for Health Solutions–Kenya (CHS) supported the buy-in and ownership of a Nairobi TB Free City Initiative by NCC government with a vision of reversing the TB epidemic in the county. The process involved a series of consultative meetings with NCC technical and political leaders, and other stakeholders that resulted into formation of a technical working group (TWG) headed by the NCC Director of Health Services. The TWG comprises membership from NCC and other stakeholders and plays advisory and supervisory roles for the Initiative.

**Results/Impact:** CHS's approach has resulted into NCC government ownership of the Initiative, and adoption of the comprehensive Search, Prevent and Treat approach. In addition, the NCC has not only allocated more funding to TB activities, but is also working with stakeholders to develop a protocol and funding proposal for activities geared towards ending TB in Nairobi. This effort will include high level lobbying with Central government and Development Partners to support a coordinated response towards eliminating TB in the city.

**Conclusions:** Engaging the city county government right from conceptualization of the initiative is critical to ensure buy-in, ownership and stewardship. This approach will ensure sustainability and political commitment towards ending TB in the Nairobi City County.



### OA-21-631-22 Maintaining TB care and management through community refills in a high HIV/TB burden setting in the era of COVID-19

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**Background and challenges to implementation:** Globally, tuberculosis (TB) claims about 4,000 lives daily. Since TB primarily affects the lungs, people with TB may be more susceptible to severe manifestations of COVID-19. Eswatini's high rate of TB/HIV puts the country at risk of experiencing a high number of COVID-19 deaths if social distancing is not incorporated into clinical protocols.

**Intervention or response:** To ensure social distancing and to minimize TB patient exposure to COVID-19, Baylor-Eswatini has adopted telephone consultation and community medication dispensing. To operationalize this modified service delivery, a nurse contacts the patient to schedule a medication delivery and sputum collection visit. During this call, if the patient expresses health concerns, a detailed medical history is taken and is documented in the medical record. The patient's TB medicines and additional medications as prescribed, are collected from the pharmacy and taken to the patient. Two to three months of TB medicines, is made available to the patient to reduce patient-health care worker (HCW) contact. Sputum for treatment monitoring is collected. On community visits HCWs use essential personal protective equipment. Patients with drug-resistant TB are given injection free treatment options, which ensures less contact with the health system. The same community based approach is used for children under five years receiving TB prevention medicines. Thirty out of thirty-four TB patients were seen in the community.

**Results/Impact:** Patients value Baylor-Eswatini's community treatment service. This delivery method alleviates travel challenges in the absence of public transport due to COVID-19.

Further, it allows HCW to get to understand community influencers (e.g., home circumstances) which effects the health of their patients and reduces the risk of nosocomial COVID-19 transmission.

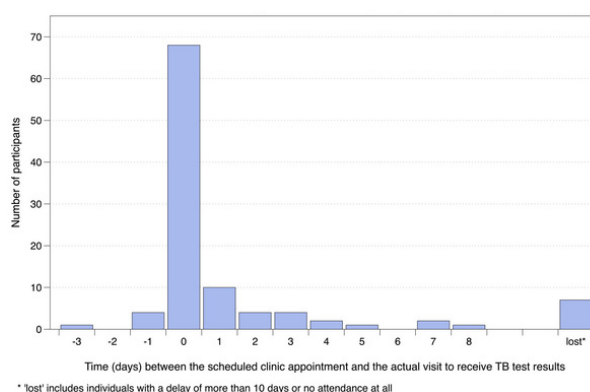
**Conclusions:** Community service delivery is resource intensive but protects a vulnerable population and ensures continuity of TB services during the COVID-19 pandemic.

### OA-21-632-22 A WhatsApp-based interactive communication strategy to reduce initial loss to follow-up among presumptive TB patients in a high-incidence setting

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**Background:** Delays and losses along the tuberculosis (TB) care cascade constitute an important challenge for TB programmes. Mobile messaging services such as WhatsApp might help mitigate this challenge. We developed and piloted a WhatsApp-based interactive communication strategy to reduce initial (pre-treatment) loss to follow-up. We aimed to investigate the uptake and use of this intervention among individuals awaiting TB test results in a high-incidence setting.

**Design/Methods:** We enrolled adults ( $\geq 18$  years) who underwent routine sputum testing for TB in two primary healthcare clinics in Khayelitsha (Cape Town), South Africa. Individuals were eligible if they owned a WhatsApp-compatible phone. Participants underwent a baseline survey and training. The intervention consisted of structured WhatsApp-based reminders and prompts sent prior to a routine clinic appointment scheduled 2-3 days after the initial (diagnostic) visit. Attendance of appointments was verified through in-person day-to-day monitoring.



[Figure. Attendance of scheduled clinic appointments among 104 presumptive TB patients enrolled]

**Results:** We approached 333 presumptive TB patients of whom 104 (31%) were enrolled. Main reasons for non-participation (N=229) were: owning a WhatsApp-incompatible phone (144; 63%), and not owning a phone (69; 30%). Participants were younger than non-participants (median age: 37 vs. 47 years); 59 (57%) were female, 95 (91%) reported TB-characteristic symptoms and 41 (39%) were HIV-infected. While all received WhatsApp reminders, 78 (75%) actively responded to prompts to

confirm or reschedule appointments; 29 (28%) opted to include a family member to receive reminders. Ninety-seven (93%) of 104 participants returned to the clinic for their TB test result (Figure).

**Conclusions:** In this high-incidence setting, uptake of a WhatsApp-based communication intervention among presumptive TB patients was low, mainly due to the lack of WhatsApp-compatible phones. However, among mostly young WhatsApp users, we observed high uptake and retention. Additional research is needed to understand whether mobile interactive messaging services including WhatsApp could impact on efforts to strengthen the TB care cascade in high-incidence settings.

## E-POSTER SESSION (EP)

### EP11 TB: HIV and diabetes comorbidities

#### EP11-197-22 Implementation of a mHealth strategy to increase linkage to and engagement in HIV care among people with tuberculosis and substance use in Irkutsk, Siberia

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**Background:** In Irkutsk, Siberia, substance-using populations face a high burden of co-infection with human immunodeficiency virus (HIV) and tuberculosis (TB). Patients in this context face considerable barriers to adequate initiation of antiretroviral therapy (ART) and engagement in care. Mobile health interventions have shown promise for increasing engagement in care for people living with HIV.

**Design/Methods:** A previously tested mHealth intervention was adapted for the Russian language and cultural context by an interdisciplinary team and named MOCT (Russian for 'Bridge'). The app provides daily reminders, queries on mood/stress levels, and messaging features. A cohort admitted at the Irkutsk TB Referral Hospital was trained on MOCT use and initiated on ART, and followed over 6 months to monitor adherence to care and clinical outcomes.

**Results:** We enrolled a cohort of 57 patients with high rates of reported prior intravenous drug use (56%) and alcohol use (82%). Surveys at 6 months (N=42 to-date) reveal optimal self-rated daily adherence for both HIV meds (95%) and TB meds (88%), with  $\geq 1$  med refill for 95% and attendance at  $\geq 1$  HIV clinic visit for 93% by 6 months.

A control group of patients (N=50) admitted at the hospital in the year prior to MOCT had similar demographics. From baseline to 6 months we observed improved mean CD4 count and viral suppression in the MOCT group ( $p < 0.01$  for both) and control group ( $p = 0.01$  for both), and a higher CD4 count (298 versus 262,  $p = 0.28$ ) and rate of viral suppression (67% versus 48%,  $p = 0.25$ ) at 6 months for the MOCT group (N=48) versus control group (N=48) so far.

**Conclusions:** MOCT usage was associated with excellent medication adherence and engagement in care among a high risk cohort. Preliminary analysis suggests improved clinical outcomes in the MOCT group versus control group.

#### EP11-198-22 Concomitant hepatitis B or C infection in patients with tuberculosis in the Netherlands: results of screening specific risk groups

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**Background and challenges to implementation:** In 2019, 74.7% (567/759) of tuberculosis (TB) patients in the Netherlands were foreign-born. The Dutch Thoracic Society recommends screening TB patients from Africa/Asia, TB patients with human immunodeficiency virus (HIV) co-infection, and intravenous drug users (IDU) with TB on hepatitis B (HBV) and C (HCV). The background prevalence of HBV (HBsAg) is estimated at 0.1% and of HCV (anti-HCV) at 0.2%; however, in migrants from endemic countries the prevalence is estimated at 5.4% and 1.4% respectively.

**Intervention or response:** Descriptive statistics were performed using data on HBV/HCV screening of TB patients registered in the National TB Register in 2019.

**Results/Impact:** Twenty-one (9.2%) of 228 HBV-tested TB patients were HBsAg positive and 8 (4.1%) of 197 HCV-tested TB patients were anti-HCV positive, of whom 2 were HCV-RNA positive. Three patients tested positive on HBsAg and anti-HCV.

Of TB patients born in Africa, 35.1% (92/262) were HBV-tested and 11 (12.0%) were HBsAg positive; 30.5% (80/262) were HCV-tested and 4 (5.0%) were anti-HCV positive. Of TB patients born in Asia, 41.1% (78/190) were HBV-tested and 5 (6.4%) were HBsAg positive; 34.2% (65/190) were HCV-tested and 1 (1.5%) were anti-HCV positive.

Of 21 HIV-co-infected TB patients, 10 (47.6%) were HBV-tested; 4 (40.0%) were HBsAg positive. Seven (33.3%) were HCV-tested; 2 (28.6%) were anti-HCV positive. One HIV-co-infected patient was HBsAg/anti-HCV positive.

Of 18 IDU, 8 (44.4%) were tested on HBV and HCV; 37.5% (3/8) were HBsAg positive, 25.0% (2/8) anti-HCV positive.

**Conclusions:** Screening TB patients on HBV and HCV resulted in the identification of a substantial number of co-infected patients and can contribute to elimination strategies set for these diseases in the Netherlands. Further efforts are needed to increase HBV and HCV testing in TB patients and additional research should further specify high risk groups for HBV and HCV infection in TB patients.

### EP11-199-22 Impact of universal tuberculosis screening (TB-Surge) on HIV case finding in selected facilities. Lessons from the TB Surge intervention in Akwa Ibom State, Nigeria

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**Background and challenges to implementation:** Akwa Ibom State in Nigeria is a major contributor to missing tuberculosis (TB) cases and also has the highest HIV prevalence rate in the country. The sero-prevalence of HIV among patients with TB is known to be higher than the general population. Interventions targeted at finding missing TB cases can also impact on HIV case finding.

**Intervention or response:** Between May-Sept. 2019, the TB-surge intervention was implemented to find missing TB cases in 12 selected secondary health facilities in Akwa Ibom. Ad-hoc staff were engaged to screen all hospital attendees for signs and symptoms of TB using a modified symptom checklist. Based on WHO recommendation, all presumptive TB without a known HIV status were linked to Provider-Initiated-Testing and Counselling (PITC). All HIV positive cases were subsequently linked to Anti-retroviral treatment (ART).

Time-Period	# presumptive TB cases identified	# tested for HIV	# new HIV positive detected among presumptive TB	Total # of new HIV positive diagnosed in the facilities	Proportion of new HIV+ve who were presumptive TB
Q1 2019 (Baseline)	1540	1091	214	893	24%
Q2 2019 (Intervention)	3838	2627	587	956	61%
Q3 2019 (Intervention)	3472	1931	422	1008	42%

[Table 1: Trend of HIV case-finding among presumptive TB Q1-Q3 2019]

**Results/Impact:** Within 5 months of intervention, 39,767 hospital attendees were screened for signs and symptoms of TB. Presumptive TB identified were 7,337 (18.4%), of which 4,402 were tested for HIV. Of the presumptive TB that had PITC, 1,072 (24%) tested

HIV positive and were linked to ART across the 12 facilities. Female presumptive TB were more likely to be HIV positive ( $p < 0.05$ ). Quarter trend analysis showed that as more presumptive TB were identified, there was a significant increase in proportion of new HIV positive patients diagnosed among presumptive TB ( $p < 0.05$ ).

**Conclusions:** Universal TB screening interventions can contribute significantly early HIV diagnosis and commencement of ART thus reducing their risk of opportunistic infections including Tuberculosis.

### EP11-200-22 An assessment of free radical oxidation of small intestine enterocyte proteins in HIV/tuberculosis co-infection

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**Background:** The aim of the study was to evaluate the degree of oxidative modification of proteins in small intestine enterocytes in patients with co-infection HIV/tuberculosis (HIV/TB) that can help to establish the effect of co-infection on the intensity of free radical processes in small intestine.

**Design/Methods:** A prospective pathomorphological study was conducted with the inclusion of 24 section cases of patients with HIV/TB (group 1) and 20 section cases of persons without gastrointestinal pathology and morphological features of tuberculosis infection (group 2).

The oxidative modification of enterocyte proteins was evaluated by red/blue (R/B) coefficient for specific coloration of acidic and basic enterocyte proteins according to Mikel-Calvo and by quantitative indices of optical density (QIOD) of specific coloration on free amino groups of proteins by A. Yasuma and T. Ichikava.

**Results:** Comparison of the obtained data revealed that the average value of the red/blue ratio for specific coloration of acidic and basic proteins according to Mikel-Calvo in group 1 was 2 times higher than in group 2  $2.06 \pm 0.012$  versus  $1.04 \pm 0.003$  ( $p < 0.05$ ). QIOD of proteins in enterocytes in group 1 was 1.7 times higher than in group 2 -  $0.314 \pm 0.0022$  in group 1 versus  $0.181 \pm 0.0022$  in group 2 ( $p < 0.05$ ).

**Conclusions:** The obtained data indicated the enhancement of processes of proteins free radical oxidation in the small intestine epitheliocytes in patients with tuberculosis/HIV with specific effects - the growth of limited proteolysis and oxidation of amino groups of proteins. This might be an important pathogenetic factor in the formation of functional failure of the small intestine due to hypoxia and prolonged intoxication, the direct pathological effect of HIV on small intestine epitheliocytes.

## EP11-201-22 Monocyte and lymphocyte ratio as a predictor of tuberculosis among people living with HIV after ART initiation

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**Background:** Early diagnosis of tuberculosis (TB) can be challenging in people living with HIV (PLWH) due to atypical presentation. A simple biomarker to predict tuberculosis may be the monocytes to lymphocytes ratio (MLR) in peripheral blood. We assessed the relationship between multiple time-updated MLR measurements and incidence of TB in PLWH after antiretroviral therapy (ART) was initiated.

**Design/Methods:** We conducted a retrospective analysis from a long-term HIV cohort in Bangkok. All participants were followed every 6 months for routine HIV care. The MLR and BMI were up-dated at least every 6 months. The CD4 cell count and HIV RNA were up-dated at least every 12 months. TB incidence with corresponding 95% confidence intervals stratified according to time-updated MLR was calculated, using MLR in quartiles. If TB was diagnosed outside of the scheduled 6-month visit, the previous MLR was used. Cox proportional hazards regression with time updated MLR was used to determine the hazard ratio of the upper 3 MLR quartiles relative to the lowest quartiles as a reference group.

**Results:** From Jan 2000 to Aug 2019, a total of 1305 PLWH were included in the analyses; 46 participants had incident TB (TB/HIV) and 1259 were in the control group. Eight hundred and one (61%) participants were male with a median age of 35.8 (IQR 30.8- 41.5) years. We found higher MLR at ART initiation in those who developed TB than in those who did not; 0.24 (IQR 0.18-0.39) vs 0.18 (IQR 0.14-0.24),  $p < 0.001$ . TB incidence rates were strongly associated with increasing time-updated MLR. In univariate model, having higher MLR increases hazard ratio of developing TB (Table1).

MLR	Total number of TB incidence	PY at risk	Rate per 1000 PYs (95%CI)	Hazard ratio (95%CI)
< 0.15	4	3,632.1	1.1 (0.4-2.9)	Ref
0.15-0.19	3	4,149.5	0.7 (0.2-2.2)	0.75 (0.17-3.35)
0.20-0.24	11	2,756.7	4.0 (2.2-7.2)	4.33 (1.37-13.63)
≥0.25	28	2,722.7	10.3 (7.1-14.9)	11.12 (3.88-31.85)
Total	46	13261	3.5 (2.6-4.6)	

[Table 1. TB incidence rates after ART initiation stratified by time-update MLR]

**Conclusions:** Increasing MLR predicted incident TB after ART initiation. The MLR can be a simple tool to stratify the risk of tuberculosis in PLWH.

## EP11-202-22 Co-morbidities in Filipino persons with active-TB disease: baseline data from the Starting Anti-TB Treatment (St-ATT) Cohort

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**Background:** Philippines ranks 3rd globally for TB incidence. The 2035 Global End TB Strategy includes the need to diagnose and manage co-morbidities in TB, but Filipino data on the prevalence and patterns of co-morbidities of malnutrition, diabetes, hypertension and anemia are scarce.

**Design/Methods:** Non-pregnant individuals aged ≥18 years, within 5 days of initiating a new TB treatment regimen in 15 public TB-DOTS clinics in three regions in the Philippines were enrolled (St-ATT Cohort ISRCTN16347615). Trained research nurses collected data and conducted clinical assessments. Diabetes was defined as HbA1c ≥6.5% or pre-existing diagnosis and/or on treatment. Hypertension was defined as >140 systolic or >90 diastolic mmHg. Moderate or severe anemia was defined as <11 mg/dL.

**Results:** Between August 2018 to February 2020, a total of 903 persons with TB were enrolled; 351 (43.4%) were malnourished (BMI <18.5 kg/m<sup>2</sup>) including 97 (10.8%) moderately (BMI ≥16.0 – 17.0 kg/m<sup>2</sup>) and 111 (12.3%) severely malnourished (BMI <16.0 kg/m<sup>2</sup>). Malnutrition (moderate or severe, BMI <17.0 kg/m<sup>2</sup>) was the most common co-morbidity (208/901, 23.1%) followed by diabetes (200/883, 22.7%), hypertension (128/865, 14.8%), then moderate/severe anemia (121/901, 13.4%). In those with complete data, the most common combination of 2 co-morbidities was malnutrition and anemia (45/848, 5.3%), followed by malnutrition and diabetes (26/848, 3.1%). Having one or more co-morbidities was more common in those with drug-resistant compared to drug sensitive TB (79/127, 61.8% vs 380/729, 54.6%,  $p=0.05$ ). HIV status was known for 527 individuals, of whom only 8 were positive.

**Conclusions:** The prevalence of multimorbidity in Filipinos with TB is common with diabetes and malnutrition being the most common and higher among persons with drug-resistant TB. Further analyses of repeated HbA1c%, weight change and blood pressure and TB treatment outcomes are planned.

### EP11-203-22 Prevalence of disseminated tuberculosis in human immunodeficiency virus infected persons admitted with sepsis at a tertiary hospital in Western Kenya

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**Background:** The current burden of disseminated Tuberculosis in adult Persons Living with Human Immunodeficiency Virus (PLHIV) is unknown in western Kenya. LF-LAM is the only test so far found to have a mortality benefit in the diagnosis of Tuberculosis.

**Design/Methods:** A cross sectional study carried out at a tertiary hospital in western Kenya for 6 months. Target population were adult PLHIV admitted with sepsis. Evaluation was done using interviewer administered structured questionnaires. Samples were collected for full blood count, urea, creatinine levels and LF-LAM. One month after recruitment, participants with positive LF-LAM were followed up.

**Results:** Three hundred and ten participants were approached and 298 recruited. Prevalence of disseminated TB was 26% (95% CI 21.2-31.4). Participants LF-LAM positive had a lower hemoglobin level and 65% were not on antiretroviral therapy at the time of recruitment. Participants with positive LF-LAM, 73% were started on anti-TBS with mortality at one month at 27%.

**Conclusions:** Using LF-LAM, one out of four PLHIV admitted with sepsis had disseminated TB. This is a high prevalence associated with high mortality. A bedside LF-LAM should be a routine diagnostic test in PLHIV admitted with sepsis and treatment should be initiated promptly to mitigate the high mortality rate.

### EP11-204-22 Is tuberculosis a major comorbidity in adolescent girls and young women living with HIV? A Case of Turkana and Homa Bay Counties, Kenya

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**Background:** People living with HIV are 20-times more likely to develop TB and the risk is higher among adolescent girls and young women (AGYW). We evaluate characteristics and outcomes of TB/HIV co-infected AGYW in Homa Bay and Turkana Counties in Kenya.

**Design/Methods:** From January to December 2018, program data for AGYW aged 10-24 years diagnosed with TB in 126 facilities were collected and analyzed. Case

records were cross-referenced from the national TB treatment electronic system. TB services and HIV testing data were analyzed. Clinical characteristics of interest were type of TB, TB/HIV co-infection, and TB treatment outcomes disaggregated by age. Data were analyzed in STATA 12.0 and presented using frequencies, proportions and mean. Pearson's chi-square was used to test for associations.

**Results:** There were 436 AGYW (0-14 years (22%), 15-19 years (37%), and 20-24 years (41%)) diagnosed with TB and initiated on treatment. GeneXpert done on 221 (51%) samples and 160 (72%) were Mycobacterium TB positive; 105 (24%) had smear microscopy, 81 (77%) were smear positive; 30 (7%) had X-ray, 29 (97%) were positive and 80 (18%) clinically diagnosed TB. Majority, 367 (84%) had pulmonary TB. Most, 430 (99%) had known HIV status [132 (30%)] HIV positive with 131 (99%) on ART. Additionally, 103 (78%) of HIV positive AGYW had pulmonary TB. About 390 (89%) completed treatment, 15(3.4%) did not complete, 18 (4.1%) lost-to-follow-up, 3 (0.7%) transferred out. Overall, 241 were bacteriologically confirmed, and 164 (68%) cured. Treatment success was 179 (74%). The case fatality ratio was 6.1% and 0.7% among HIV positive and negative AGYW respectively,  $p = 0.001$ .

Factor/Level	10-14 years	15-19 years	20-24 years	Total
Pulmonary TB	75 (77.3)	142 (88.8)	150 (83.8)	367 (84.2)
Extra-Pulmonary TB	22 (22.7)	18 (11.3)	29 (16.2)	69 (15.8)
Bacteriologically tests (GeneXpert and Smear Microscopy)	58 (18)	124 (38)	144 (44)	326 (75)
MTB positive of bacteriological tests	35 (12)	100 (81)	106 (74)	241 (74)
GeneXpert Done	40 (41.2)	83 (51.9)	98 (54.7)	221 (50.7)
Positive	26 (26.8)	20 (12.5)	86 (48.0)	132 (30.3)
On ART (out of positives)	26 (100)	20 (100)	85 (98.8)	131 (99.2)
Cured	24 (68.5)	67 (67)	73 (68.8)	164 (68)
Treatment Completed	61 (62.9)	82 (51.2)	83 (46.4)	226 (51.8)

[Table.]

**Conclusions:** A third of AGYW diagnosed with TB were HIV positive, being higher than the general population in Kenya, at 26% overall and 14% in pediatrics. There is need to integrate TB services within AGYW service points for early case detection and treatment

### EP11-205-22 Is it necessary to screen for tuberculosis in diabetes patients and how to do it? An endocrinologist-based questionnaire survey in Hunan Province of China

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**Background:** Diabetes (DM) is known to increase the risk of active tuberculosis (TB) approximately three fold, and contributes to adverse TB treatment outcomes. WHO and The Union have launched a new ‘Collaborative framework for care and control of DM and TB’, with one of the main activities being the routine implementation of bidirectional screening of the two diseases. However, the limited literature suggests that endocrinologists don’t seem to be actively screening for TB in DM patients. We therefore launched this questionnaire survey among endocrinologists.

**Design/Methods:** We selected 14 third-level public general hospitals (PGHs), 13 second-level-PGHs, 5 first-level-PGHs in Hunan province of China, using a stratified cluster sampling method. The anonymous questionnaire survey was conducted among all endocrinologists in selected hospitals. Finally a total of 277 valid questionnaires were recovered.

**Results:** 173 (62.5%) endocrinologist considered it necessary to screen TB initiatively for first-time-visit DM patients (initiative-screen) and 80.9% (140/173) of them considered it necessary to screen TB regularly for follow-up DM patients (regular-screen).

In their actual work, 197 (71.1%) endocrinologist performed screening-TB only for DM patients with suspected symptoms. And only 23 (8.3%) endocrinologists thought that they had implemented initiative-screen and only 9 (2.9%) implemented regular-screen. But 196 (70.7%) doctors had encountered DM patients who diagnosed as TB without symptoms.

For the possible causes of DM patients who didn’t undergo TB screening, the top three reasons are „patients refused (76.5%)“, „patients didn’t have related symptoms (46.9%)“, „the institution has not carried out TB-related tests (35.7%)“. And the three most common reasons for DM patients refusing TB-screening may be „the patients have no relevant symptoms and don’t think they may have TB (88.1%)“, „the patients don’t understand the relevant knowledge of DM and TB (76.9%)“ and „Economic reasons(72.2%)“.

**Conclusions:** Endocrinologists in PGHs haven’t paid enough attention to the implementation of screening TB in DM patients, Relevant departments need to develop guidelines or expert consensus to guide or restrict.

### EP11-206-22 Prevalence of malarial and HIV co-infection amongst TB presumptive and asymptomatic children <5 years of age in Western Kenya

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**Background:** While the intersection between HIV & TB is well documented, despite the high burden of tuberculosis (TB) and malaria among children aged <5 years, co-infection data are lacking. We assessed malaria infection and HIV prevalence amongst asymptomatic and children with presumptive TB in Western Kenya.

**Design/Methods:** Children aged <5 years with clinical symptoms suggestive of TB\* and abnormal chest x-ray findings were enrolled with asymptomatic controls in Kisumu County, Western Kenya between October 2013 – August 2016 from inpatient and outpatient settings. Among symptomatic children, <8 different specimens were tested for Mycobacterium tuberculosis complex by Xpert MTB/RIF and mycobacterial culture; children were classified with TB according to consensus research case definitions\*\*. Asymptomatic children were recruited as controls. Blood smear microscopy and/or polymerase chain reaction (PCR) was used to diagnose malarial infection. HIV rapid serologic tests or dried blood spot PCR was used to diagnose HIV.

Characteristics	TB symptomatic children (n=256)**				TB asymptomatic children (n=45)	Total (n=301)
	Confirmed TB (n=30)	Unconfirmed TB (n=61)	Unlikely TB (n=165)	TB symptomatic total (n=256)		
Age (years), median (IQR)	1.9 (1.3)	2.1 (2.4)	2.4 (2.6)	2.1 (2.6)	0.9 (1.2)	2.0 (2.6)
Malaria infection status, n (%)						
Positive	2 (6.7)	7 (11.5)	17 (10.3)	26 (10.2)	4 (8.9)	30 (10.0)
Negative	7 (23.3)	23 (37.7)	33 (20.0)	63 (24.6)	4 (8.9)	67 (22.3)
Malaria & HIV co-infected, n (%)						
Positive	0 (0.0)	2 (3.3)	3 (1.8)	5 (2.0)	1 (2.2)	6 (2.0)
No co-infection, n (%)	20 (66.7)	32 (52.5)	137 (70.9)	169 (73.5)	36 (80.6)	205 (68.3)

\*Confirmed TB, bacteriological confirmation with ≥1 respiratory specimen. Unconfirmed TB, bacteriological confirmation not obtained and having ≥2 of the clinically symptoms/signs suggestive of TB, chest x-ray consistent with TB, close TB exposure, immunological evidence of TB infection, or response to TB treatment. Unlikely TB, bacteriological confirmation not obtained and criteria for unconfirmed TB not met.  
 \*\*34 Children were designated as unclassifiable according to research clinical case definitions, and 14 children were further restricted due to lack of malaria testing results.  
 \*\*\*Symptomatic children, persistent cough, fever, malnutrition despite therapy, or persistent cervical lymphadenopathy.

[Table. Demographic and clinical characteristics]

**Results:** We enrolled 256 children with TB symptoms and 45 asymptomatic children\*\*\*. Among symptomatic children, 11.7% (n=30) had confirmed TB, 23.8% (n=61) unconfirmed TB, and 64.5% unlikely TB (n=165). Malarial infection was confirmed in 10.2% (n=26) of symptomatic children [6.7% (n=2) with confirmed TB, 11.5% (n=7) with unconfirmed TB, 10.3% (n=17) with unlikely



TB] and 8.9% (n=4) of asymptomatic children. HIV prevalence was higher in symptomatic children (24.6% vs 8.9%), with the highest prevalence amongst children with unconfirmed TB (37.7%, n=23). Symptomatic children with unconfirmed TB had the highest prevalence of both malaria & HIV co-infection (3.3%, n=2).

**Conclusions:** Prevalence of malarial infection & HIV was highest among symptomatic children, particularly in those with unconfirmed TB. Previous research has shown malarial infection could potentially influence TB diagnostic performance in this age group and should be considered when attempting to diagnose pediatric TB, especially in presumptive clinical cases without microbiological confirmation or immunological markers of TB infection.

### EP11-207-22 Incidence of hypokalemia among DR-TB patients receiving delamanid-containing regimen in Lesotho

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**Background:** Delamanid, a group C drug which is known for its excellent safety profile and the least toxic agents used in the treatment of DRTB. Delamanid is used at an alarming rate at the MDRTB hospital in Lesotho because it has no drug-drug interaction when co-administered with certain ART such as tenofovir, efavirenz and lopinavir/ritonavir. This is especially important in the country considering the high HIV prevalence (25.6%) and more than 70% of DRTB patients co-infected with HIV/AIDS. Delamanid has shown some QTc prolongation during treatment and being fully aware that hypokalemia is a possible cause of QTc prolongation, it is important to determine the incidence of hypokalemia in patients receiving delamanid to avoid increased morbidity and mortality in this group.

**Design/Methods:** The study was aimed to assess the incidence of hypokalemia in DRTB patients receiving delamanid-containing regimen among 2019 cohort. A total of 158 patients were followed up within the period of 1 year for their serum potassium level at baseline and during treatment. Body weight and other confounding factors such as vomiting, use of Lasix, diarrhea and excessive sweating were also taken into consideration.

**Results:** Among 155 patients who were followed for hypokalemia, 50.3% had hypokalemia, defined as serum potassium less than 3.5mmol/l and mean serum potassium at time of diagnosis was 3.15mmol/l. The diagnosis of hypokalemia was noticed to have occurred more during the 1st and 2nd month of treatment. Multivariate analysis of risk factors for hypokalemia revealed delamanid and vomiting/Use of Lasix as 2 possible factors.

Variables	Number of patients
Baseline hypokalemia	16
Follow-up hypokalemia	78
vomiting while on delamanid	14
use of lasix	18

[Table.]

**Conclusions:** Based on this finding, it is important to monitor serum potassium levels in DRTB patients taking delamanid containing regimen to reduce morbidity and mortality and a broader study may need to be conducted to solidify this evidence.

### EP12 Approaches to paediatric TB prevention, diagnosis and treatment

#### EP12-208-22 Comparison of neurocognitive assessment in children with TB meningitis and healthy controls in Pune, India

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**Background:** Tuberculous Meningitis (TBM) in children may adversely impact brain development. The Mullen Scales of Early Learning (MSEL) is a well-established measure used to assess multiple domains of early cognitive development. It has not previously been used in TBM or in India. Our study's objective was to compare performance on the MSEL between children with TBM to healthy controls in India.

**Design/Methods:** A total of 40 children, 20 with possible, probable or confirmed TBM and 20 age- and gender- matched controls between 6–72 months of age

were included. MSEL was administered prior to TBM treatment initiation. Median MSEL raw scores and mean MSEL T-scores were compared for each domain using the sign-ranked test.

**Results:** Median (IQR) age was 32(14–57) months, and 24 (60%) were males. Median (IQR) of all five domain's scales raw scores and T-Scores were significantly higher in controls than cases, as follows: Gross Motor (27 v/s 13, p-value =0.03); T-Scores (41 v/s 20, p-value < 0.001); Visual Reception T-Scores (38 v/s 20; p-value =0.01); Fine Motor T-Scores (45 v/s 20; p-value =0.01); Receptive Language T-Scores (40 v/s 20; p-value =0.001); Expressive Language T-Scores (43 v/s 29; p-value =0.001). Overall, median T-scores for controls ranged from low average to average when compared with US based norms (T-score of 40-60 defines MSEL average range for normally-developing US children), whereas median T-scores for children with TBM were impaired.

**Conclusions:** This is the first study to compare neurocognitive performance among children with suspected TBM to healthy controls using the MSEL in India. Matched controls had significantly higher scores suggesting adverse effects on neurocognitive function resulting from TBM. Given that little is known about the degree to which these problems persist and affect long-term quality of life, longitudinal assessments are needed to understand the long-term impact of this disease process.

### EP12-209-22 Effect of community-based interventions on childhood tuberculosis treatment outcomes in hard-to-reach areas of Southern Nigeria

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**Background and challenges to implementation:** Tuberculosis (TB) treatment outcomes are indicative of the quality of TB services. While the WHO target for Treatment Success Rate (TSR) is  $\geq 90\%$ , Nigeria currently achieves 86% TSR for DS-TB cases. TSR for childhood DS-TB is not routinely reported but studies have shown a range of 83-93% in southern Nigeria and hard-to-reach areas may likely suffer far worse outcomes than others. DAHW-German Leprosy Tuberculosis Relief Association Nigeria is implementing the TB REACH wave 5 scale-up project for community-driven active case finding in hard-to-reach areas of southern Nigeria. Project aims include improving treatment outcomes using community-based interventions in selected area.

**Intervention or response:** Intervention involved six purposively selected local government areas (LGAs) in two States with perennially low TB notification (and four control LGAs) in southern Nigeria, from 2017 to 2019. In the intervention LGAs, an output-based approach was

employed: the sum of NGN 8,000 (USD 21) was given to the DOT provider and the ward/local community committee for supporting follow-up and addressing treatment interruption leading to successful treatment completion. Other interventions included: advocacy, community engagement with chest camp activities, intensive monitoring and supervision, all done in close collaboration with LGA TB supervisors. Prompt reporting and linkage of diagnosed patients to treatment was facilitated by SMS/WhatsApp notification of results. A cross-sectional analysis of data extracted from the reported National TB program's treatment outcomes from January-2016 to December-2018 cohort was done.

**Results/Impact:** In the intervention LGAs, TSR for children with TB increased from 40% (2/5) to 97% (70/72) but declined from 100% (5/5) to 86% (6/7) in the control LGAs within the period.



[Figure. Childhood TSR in intervention LGAs 2017-2019]

**Conclusions:** Childhood TB treatment outcomes markedly improved through targeted community-based interventions. We recommend that context-specific interventions to improve treatment outcomes such as conditional cash transfers linked to treatment completion be considered.

### EP12-210-22 Fine needle aspiration biopsy of peripheral lymph nodes in children in a high TB incidence setting: practical experience in a referral hospital

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**Background:** Peripheral lymphadenopathy occurs commonly in children. Fine needle aspiration biopsy (FNAB) is an often performed diagnostic procedure, and is particularly useful in high tuberculosis incidence settings. We describe the use of FNAB and outcome for peripheral lymphadenopathy in children in a routine clinical setting.

**Design/Methods:** This was a retrospective study done at Tygerberg Hospital, Cape Town, South Africa of children (<13 years) who had a FNAB for peripheral lymphadenopathy from July 2012 to June 2014. Demographic, clinical, treatment and follow-up data were retrieved from patient folders; FNAB and special investigation results were obtained from the laboratory database. Ethics approval was obtained.

**Results:** The median age of the 173 children included was 37 (IQR 13-75) months; 20 (11.5%) were HIV-positive. The median duration of lymphadenopathy was 14 (IQR 3-60) days. Most FNABs were done in the neck (131; 76%) and axillary areas (34; 20%). FNAB provided a result in 165 (95%) cases; in 8 (5%) children FNAB was insufficient for diagnosis. Mycobacterial aetiology was diagnosed in 84 (49%); 49 (58%) were culture-confirmed (37 *Mycobacterium tuberculosis*, 10 *M. bovis* BCG, 1 both *M. tuberculosis* and *M. bovis* BCG, and 1 non-tuberculous mycobacterium). Reactive lymphadenopathy was diagnosed in 56 (32%), neoplastic disease in 6 (4%) and other pathology in 19 (11%) cases. Additional special investigations changed FNAB diagnosis or led to an additional diagnosis in 8 (5%) children. Overall, 70/84 (83%) with mycobacterial aetiology and all neoplastic disease cases received the correct treatment. Follow-up appointments were arranged in 144 (83%) patients.

**Conclusions:** In a high tuberculosis burden area, a single FNAB provided a diagnosis in the majority of cases in a routine referral setting; FNAB remains a safe and useful investigation. Follow-up of children to initiate appropriate treatment could improve.

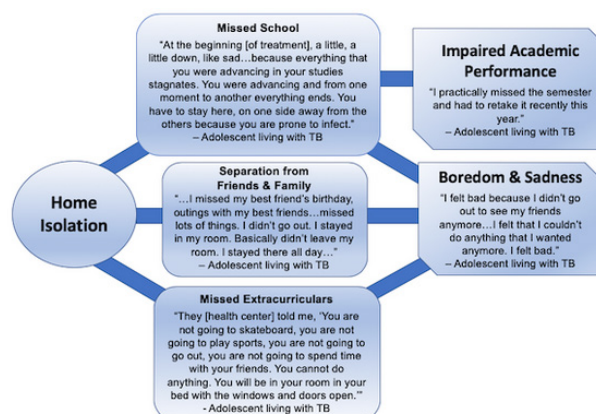
### EP12-211-22 The adverse effects of prolonged home isolation on adolescents with tuberculosis in Lima, Peru: a qualitative study

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**Background:** The Peruvian Ministry of Health mandates home isolation for patients with tuberculosis (TB) for a minimum of two months before they can return to school. However, the majority of people with TB become non-infectious in less time. We hypothesized that prolonged isolation during TB treatment may negatively impact adolescents' social, psychological, and educational development.

**Design/Methods:** Peruvian study workers conducted individual, in-depth, semi-structured interviews in Lima with 34 adolescents who received treatment for drug-susceptible pulmonary TB, as well as 15 health providers from health centers working in TB prevention and care. Five investigators individually performed conventional content analysis; interrater agreement was assessed by double-coding ten percent of the transcripts and was found to be  $\geq 90\%$ . Two of the authors identified themes from the codes through consensus.

**Results:** Forty-nine interviews were included in this analysis. Adolescents overwhelmingly reported negative impacts of home isolation on their education and social well-being. Adolescents attributed negative emotions, such as boredom and sadness, to prolonged home isolation and a loss of social connection with family and friends. For some adolescents, sick leave due to TB resulted in the loss of an entire semester or year of schooling.



[Figure.]

**Conclusions:** In Lima, Peru, adolescents with TB are generally isolated at home for 2 months, even though most people with TB become non-contagious long before then. The negative impact of this practice on adolescents highlights the need for evaluating mental health and academic outcomes among a larger sample of adolescents undergoing TB treatment.

### EP12-212-22 Feasibility of testing pediatric samples for TB diagnosis: "implications of the pre-analytical phase, lessons learned and challenges"

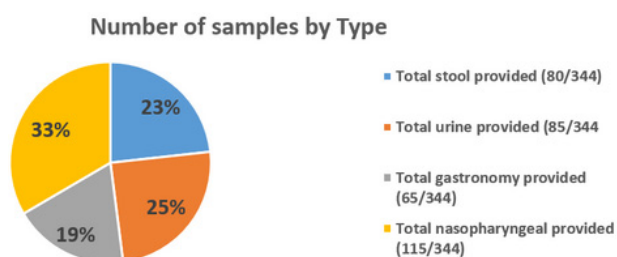
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**Background:** Pediatric tuberculosis (TB) remains a significant cause of death globally, mainly due to difficulties in diagnosis. TB laboratory confirmation is only

obtained in a minority of cases due to the difficulty in obtaining samples for microbiological examination, and the often pauci-bacillary nature of the disease. The main objective of this analysis was to evaluate the feasibility and performance of a combined multi-sample pediatric TB diagnostic approach.

**Design/Methods:** This was a cross-sectional study embedded in an active case finding strategy which took place in Manhiça district, southern Mozambique in 2018. We included symptomatic children < 12 years who were household contacts of a microbiologically confirmed TB case. They were evaluated at the local hospital and requested to provide four samples in the same day: nasopharyngeal aspirated (NPA), gastric aspirate (GA), urine and stool. All samples were tested by Xpert Ultra and culture.

**Results:** Of the 161 patients recruited, 85% delivered at least one sample (137/161). Twenty percent (28/137) provided the four requested samples, 31% (42/137) provided 3, 39% (54/137) 2 and 16% (23/137) only 1 sample. A total of 344 samples were received (Figure): 3.7% (13/344) were rejected due to spillover, 3.7% (13/344) of NPA had less than 1 ml, and 1.2% (4/344) AG were empty. Only 6 (1.8%) of all collected samples were positive by Xpert Ultra (3 NPA and 3 stools from different patients) and only 1/344 was confirmed by culture liquid.



[Figure.]

**Conclusions:** Our findings reveal that the laboratory diagnosis of pediatric TB remains a challenge due to the difficulties in each of the preanalytical steps: sample collection, transport and storage. Urine and NPA were the ones associated with bigger challenges in preanalytical stages. We strongly recommended putting attention, not only during the collection process to ensure enough volumes and quality, but also during transport and storage.

## EP12-213-22 A systematic review of the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for the diagnosis of tuberculous meningitis and lymph node tuberculosis in children

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**Background:** Xpert MTB/RIF and Xpert Ultra are rapid molecular tests that detect tuberculosis in children with signs and symptoms of tuberculosis. To inform updated WHO Consolidated Guidelines on Tuberculosis Diagnosis (2020), we performed a systematic review on the diagnostic accuracy of these tests in children presumed to have tuberculous meningitis and lymph node tuberculosis.

**Design/Methods:** We searched databases to 29 April 2019 without language restriction for studies evaluating Xpert MTB/RIF or Xpert Ultra in cerebrospinal fluid, or lymph node specimens obtained by fine needle aspiration or surgically. Reference standards were culture or a composite reference standard for tuberculosis. Two authors independently extracted data and assessed study quality using QUADAS-2. For each target condition, we used the bivariate model to estimate pooled sensitivity and specificity with 95% confidence intervals. We planned to stratify analyses by reference standard. However, owing to insufficient data, we did not perform a meta-analysis using a composite standard.

**Results:** We included 10 datasets (423 participants) for tuberculous meningitis and 10 datasets (423 participants) for lymph node tuberculosis. No studies identified evaluating Xpert Ultra. For tuberculous meningitis, Xpert MTB/RIF pooled sensitivity and specificity against culture were 54.0% (27.8 to 78.2) and 93.8% (84.5 to 97.6). For lymph node tuberculosis, Xpert MTB/RIF pooled sensitivity and specificity against culture were 90.4% (55.7 to 98.6) and 89.8% (71.5 to 96.8). Risk of bias was generally low for all domains, except unclear for the reference standard, because many studies collected only one specimen for culture.

**Conclusions:** Xpert MTB/RIF sensitivity for tuberculous meningitis is not adequate to withhold treatment based on the test result alone and the entirety of the clinical information must be considered. Xpert MTB/RIF was sensitive for lymph node tuberculosis. Xpert MTB/RIF's low specificity for tuberculous meningitis and lymph node tuberculosis may reflect limitations of culture as a reference standard for paucibacillary tuberculosis.

### EP12-214-22 Pediatric TB care cascade: an assessment of knowledge, attitude and practice among health care providers in Pune district, India

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**Background:** Around 20% of World's total TB cases occur in India, with estimated 10% of pediatric cases among them. But only six percent of these are being reported, resulting in many undiagnosed, untreated TB and many preventable deaths in younger population.

**Design/Methods:** Probability Proportional to Size sampling was used to select 151 Front Line Workers (FLWs) and 60 Private doctors. Universal sampling was used to select all (30) Govt. Medical Officers and National TB Elimination Program (NTEP) staff. Total 241 Health Care Providers (HCP) were selected for study.

**Results:** Around 90% of Govt. doctors and NTEP staff chose sputum smear as single key test for TB diagnosis while nearly half of the FLWs and private doctors preferred it, while rest of them opted for chest X ray. Only 20% of the private doctors were maintaining separate records of TB patients, as compared almost all Govt. HCPs. Less than half of the private doctors screening the contacts of TB patients' vis-a-vis done by almost all Govt. doctors. Around 65% of Govt. doctors and 24% of private doctors encounter pediatric TB patients. Most of them (>80%) face the challenge of inability of children to expectorate sputum for testing, followed by difficulty in diagnosis of extra pulmonary cases and availability of specialized facilities. While treating pediatric TB, more than half of the HCPs face problems with drug form and dosage calculations followed by non-compliance of patients (17 to 55%). Nearly half of the HCPs (41 to 52%) expressed that low knowledge among HCPs leading to inadequate implementation of INH prophylactic therapy. More than half of the HCPs (54%) have not undergone any training about pediatric TB management.

Challenges faced for diagnosis of pediatric TB (multiple response)	N=239	%
Availability of facility for diagnosis	97	40.6
Children can't give sputum	204	85.4
Extra pulmonary cases difficult to diagnose	107	44.8
Tuberculin test not reliable	63	26.4
No standard diagnostic algorithm	16	6.7
Others	10	4.2

[Table: Challenges faced for diagnosis of pediatric TB by HCPs.]

**Conclusions:** The study emphasizes need of capacity building of HCPs especially private doctors on pediatric TB management and provision of specialized diagnostic facilities like gastric lavage for sputum collection.

### EP12-215-22 Knowledge, attitudes and practices on childhood TB among health care workers in sub-Saharan Africa and South-East Asia

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**Background:** Reducing childhood TB mortality requires the deployment of diagnosis tools at peripheral healthcare level to enhance case finding and access to treatment. We assessed the knowledge and training of Health Care Workers (HCW), their perceptions and experience of childhood TB activities at district hospital (DH) and primary healthcare center (PHC) level, in Cambodia, Cameroon, Cote d'Ivoire (CI), Sierra Leone (SL) and Uganda, as part of the TB-Speed Decentralization study.

**Design/Methods:** We conducted a self-administered Knowledge-Attitudes-Practices (KAP) survey in HCW from five DH and 20 PHC. We computed knowledge levels as 4 sub-scores (epidemiology, diagnosis, treatment, prevention, /4 or 5 points) and 1 overall score (/18 points, sum of sub-scores), attitudes as 5 sub-scores (emotional, cognitive, behavioral, satisfaction, community perception, /4 points) and 1 overall score (/4 points, mean of sub-scores), and described practices as percentages.

**Results:** Of 636 eligible HCW, 497 (78%) participated: 63.3%, 69.7%, 45.5%, 43.0% and 58.0% were PHC-level respondents in Cambodia, Cameroon, CI, SL and Uganda, respectively. Their median age ranged between 31.0 and 40.0 years.

Table 1 summarizes some of the key KAP results. Overall knowledge scores ranged between 7.4 and 11.8 out of 18, with diagnosis sub-scores systematically at or below average. Attitudes, although varying according to study countries, were overall favorable towards childhood TB diagnosis. A third or less of HCWs reported diagnosing children with TB or presumptive TB a few times a week.

**Conclusions:** Knowledge, attitudes and practices on childhood TB largely differed among HCWs of the five countries, highlighting different awareness and experience of childhood TB case management. This survey contributed to identifying potential barriers and facilitators to the decentralization of childhood TB diagnosis.



		Cambodia (n=30)	Cameroon (n=99)	Côte d'Ivoire (n=99)	Sierra Leone (n=93)	Uganda (n=176)
HCW profile	Nurses or clinicians (%)*	30.0	39.4	25.2	58.1	51.1
	Mean overall score (/18)	9.9	10.0	7.4	9.0	11.8
Know- ledge	Diagnosis sub-score (/5)	2.3	2.4	1.6	2.0	2.7
	Knowledge of Xpert as a diagnosis test for childhood TB (%)	50.0	47.5	21.2	38.7	68.2
	Mean overall score (/4)	3.3	2.8	2.9	2.8	3.1
Attitudes	Reluctance to collect and test stools for childhood TB (%)	56.7	25.3	25.3	34.5	42.0
	Reluctance to collect induced sputum/throat aspirates (NPA) for TB diagnosis in children (%)	70.0	25.3	36.4	36.6	46.1
	Diagnose children with TB or presumptive TB few times a week (%)	13.3	18.2	15.2	34.4	27.8
Practices	Never start children on TB treatment without laboratory confirmation (%)	70.0	81.8	41.4	58.1	36.9

\* Excluding nurse assistants and midwives

[Table 1.]

## EP12-216-22 Improving child tuberculosis notification through innovative case-finding approaches in hard to reach areas of Delta State, Nigeria

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**Background and challenges to implementation:** Despite the high prevalence of tuberculosis (TB) in Delta State, Nigeria, the proportion of TB cases notified in children compared to all TB cases has remained below 5%. Persistent barriers include poor access and weak child TB diagnostics. We aimed to increase the number of children diagnosed with TB using a multi-pronged collaborative intervention in hard-to-reach areas.

**Intervention or response:** The intervention implemented in quarter 3 of 2018 was 4-fold:

- (1) clinician engagement using social media;
- (2) continuous medical education in partnership with the Nigerian Medical Association using the national childhood TB screening algorithm;
- (3) expanded access to free childhood chest x-ray (CXR) and reports from 2 to 15 centres in 15 of 25 Local Government Areas - children were transported to x-ray centres and radiologists reported on CXRs; and

(4) demand creation through targeted community outreach by engaging gate-keepers in “higher risk” communities – those hard-to-reach, having high TB burden, low child TB case notification and high prevalence of childhood malnutrition.

New TB cases were counted using the National TB Programme Monitoring and Evaluation system by year before, during and after the intervention.

**Results/Impact:** The number of child TB cases increased 1.5 fold (73 to 107 cases) from 2017 to 2018, and a further 3.3 fold (107 vs 350) from 2018 to 2019. Similarly, the proportion of TB cases notified in children as compared to all TB cases rose from 3.2% to 4.4% to 12.2% over the same 3-year period (table). For 2018-2019, cases by quarter are summarized (table).

Annual Child TB Notification				Quarterly Child TB Notification				
Year	All forms of TB	Child TB Cases	Child proportion	Quarter	All forms of TB	0-4 years	5-14 years	Child proportion
2013	2814	83	2.9	Q1 2018	580	5	15	3.5
2014	2403	41	1.7	Q2 2018	554	0	21	3.8
2015	2349	77	3.3	Q3 2018	638	6	22	4.4
2016	2235	76	3.4	Q4 2018	682	25	13	5.6
2017	2258	73	3.2	Q1 2019	701	22	20	6.0
2018	2454	107	4.4	Q2 2019	664	35	34	10.4
2019	2863	350	12.2	Q3 2019	799	79	67	18.3
				Q4 2019	697	45	48	13.3

[Table. Annual and quarterly trend of child TB case notification]

**Conclusions:** Both the number of child TB cases and the proportion of TB cases notified in children compared to all cases increased following implementation of a multi-pronged intervention in these high risk communities. A similar strategy implemented on a national scale in Nigeria could have a major public health impact.

## EP12-217-22 Progress towards updated policy guidance for WHO recommended best practices in paediatric TB/RR-TB care

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**Background and challenges to implementation:** In 2018, the World Health Organization launched a revised ‘Roadmap towards ending TB in children and adolescents,’ outlining key actions that should be taken at country level to optimally prevent and treat TB in these age groups. Information on country level adoption of WHO guidance on paediatric TB/RR-TB is lacking.

**Intervention or response:** The #StepUpforTB 2020 study aims to assess policy-adoption of international best practices and innovations on TB diagnosis, prevention and treatment in 43 high TB burden countries by the end of December 2019. A semi-structured questionnaire was

used to interview National TB Programme managers or assigned focal points and supported by a desk review of national policy documents. The overall response rate was 84%.

**Results/Impact:** Survey results show that in 34/36 countries, all children with presumptive TB are eligible for rapid molecular diagnostics as the initial diagnostic test. In 27/36 countries the national policies indicate routine use of an injectable-free regimen for children with mild RR-TB disease, and 32/36 countries have already ordered paediatric second-line drug formulations from the Global Drug Facility. 33/36 and 27/36 countries are in line with WHO recommendations for use of bedaquiline in children 6 years and older and delamanid in 3 years and older respectively. Paediatric contacts under 5 years irrespective of HIV status are prioritized for TB preventive therapy (TPT) in 34/36 countries; 17/36 countries additionally target children who are household contacts of clinically diagnosed drug-sensitive TB cases. The majority of countries (32/36) do not require TST or IGRA before starting TPT in children under 5 years.

**Conclusions:** Results show promising policy uptake of optimal strategies for paediatric latent TB infection and disease management. Further research is needed to assess other barriers to adoption of pediatric best practices, as well as evaluating policy implementation in routine clinical care.

### EP12-218-22 Reasons and routes of admission among hospitalised children and adolescents with rifampicin-resistant tuberculosis receiving treatment in South Africa's 'injectable-free era'

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**Background:** The South African Department of Health released a ground-breaking policy in September 2018 recommending injectable-free treatment for everyone, including children and adolescents, with rifampicin-resistant tuberculosis (RR-TB). Global emphasis on paediatric RR-TB case detection has highlighted decentralisation of care from specialist hospitals to primary care level.

We report on a cohort of hospitalised children and adolescents with RR-TB in Cape Town over the past 18 months.

**Design/Methods:** We retrospectively reviewed hospital records for individuals aged <16 years admitted to the paediatric wards of Brooklyn Chest TB Hospital (BCH) between September 2018 and February 2020. We described referral pathways and reasons for BCH admission among those with clinical or confirmed RR-TB.

**Results:** Among 173 children and adolescents admitted over the study period, 64 (37%) had RR-TB, of which eleven (17%) were HIV-positive. Among 41 (64%) children aged ≤5 years, 8 (13%) aged 6 to 9 years and 15 (23%) aged 10 to 15 years, RR-TB was microbiologically confirmed in 22 (54%), five (63%) and 15 (100%) individuals, respectively; the rest were clinically diagnosed. Fourteen (22%) patients were admitted directly from primary care facilities while the rest were transferred to BCH from other hospitals. Twenty-four (38%) patients were referred as 'standard procedure', 23 (36%) were admitted due to 'parent preference' or 'social reasons', 6 (9%) had severe RR-TB disease requiring hospitalised care, and the remainder (17%) had multifactorial problems. Fifty-eight (91%) patients initiated anti-TB treatment before BCH admission (45 [78%] in hospital). No-one received injectable-containing treatment after admission to BCH and 44 (69%) received regimens containing bedaquiline, delamanid and/or linezolid.

**Conclusions:** Children and adolescents with RR-TB have benefited from the national injectable-free policy. Hospitalised management of patients with RR-TB is sometimes unavoidable however, with adequate training, oversight and sustained specialist support, decentralisation of quality paediatric RR-TB care will likely benefit many patients and families.

### EP13 Improving all steps of the TB cascade of care: from identification to beyond treatment

#### EP13-219-22 Six-month vital status of presumptive TB patients at 20 community health centers in Uganda

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**Background and challenges to implementation:** Data on outcomes of patients with presumptive TB in high-burden settings are limited. We sought to assess 6-month vital status and characterize subsequent TB care for adults (n=8,281) who initiated TB diagnostic evaluation at 20 community health centers in Uganda between October 2018 and October 2019.



**Intervention or response:** TB treatment registers were first reviewed to identify patients who initiated treatment during the study period and had a known 6-month vital status. All other patients who submitted sputum for TB testing were traced through a combination of phone calls using numbers extracted from TB registers or home visits by trained local village health team members (if unreachable by phone). Vital status was collected if patients or family members were contacted, and information on further TB testing and treatment was also collected if the patient was contacted.

**Results/Impact:** Vital status was obtained for 4,080 patients tested for TB through a combination of treatment outcome review (6.5%), phone calls (46.8%) and home visits (46.6%). Overall, 179 (4.4%) patients had died within 6 months. Among 216 patients with confirmed TB, seven additional deaths were identified through tracing and mortality increased from 6.5% (14/216) to 9.7% (21/216). Among 3,864 patients without confirmed TB on initial evaluation, 158 (4.1%) had died and 145 (3.8%) reported a new TB diagnosis. Treatment had been initiated in 55/145 (37.9%) patients with a new TB diagnosis. **Conclusions:** Mortality is high among patients initiating TB diagnostic evaluation in Uganda, likely due to failure to diagnose and treat TB. These data highlight the need for rapid and more sensitive diagnostics at lower level health centers to facilitate TB diagnosis and linkage to TB treatment.

### EP13-220-22 Pilot experience of self-administered treatment for people affected by tuberculosis in Conakry, Guinea

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**Background and challenges to implementation:** Guinea, with 12 million population and 176 tuberculosis (TB) estimated cases/100,000 inhabitants faces important TB control challenges. Around 50% of people affected by TB are detected in the Conakry the capital, where patients follow-up faces difficulties due to accessibility to the health facilities, infectious diseases outbreaks and social unrest. The National Tuberculosis Programme and Damien Foundation developed a pilot experience of self-administered treatment (SAT) in order to ensure adherence to treatment if circumstances hinder direct treatment observed (DOT) treatment by health staff at health facilities.

**Intervention or response:** In 2018, two health facilities of Conakry were selected, health staff and community volunteers were trained. A mechanism of follow-up by

monthly visits to the households were organized, as well as phone calls to encourage SAT for consent patients enrolled. The study took place from October 2018 – December 2019. During the household visits, contact members were screened for TB. We used Open Data Kit (ODK) for collection of data, connected to a password protected server.

**Results/Impact:** We enrolled 254 people affected by bacteriologically confirmed TB (BCT). Eight patients are under treatment. Treatment outcomes were: 234(95.1%) cured, 2(0.8%) treatment completed, 6(2.4%) died and 4(1.6%) failure. 1537 household contacts were listed, 1241(81%) were screened for TB during home visit. There were 29 (2.3%) presumptive TB cases, among them sputum samples were collected for 24(83%), five(19%) were confirmed with pulmonary TB. 205 children under five years old were enregistered and 129 (63%) were put on isoniazid preventive treatment (IPT).

**Conclusions:** Our pilot experience on SAT with the above combine interventions ensured a cured rate of 95.1%. Also, performing household visits helped to screen 81% contacts for TB and catch up the IPT for many children under five years. This experience can be implemented in other health facilities where people affected by TB have difficult access to health facilities.

### EP13-221-22 Pathway for TB care seeking and treatment: a multi-country analysis among tuberculosis patients in Ethiopia, the Philippines, and Uganda

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**Background:** Reducing the chain of tuberculosis (TB) transmission in high-burden countries depends on timely diagnosis and treatment initiation. This multi-county study by MEASURE Evaluation, supported by USAID, examined the patient pathway from the onset of symptoms suggestive of TB to initiation of TB treatment, to better understand where bottlenecks occur that can lead to delays in treatment initiation.

**Design/Methods:** Current TB patients were asked a series of questions to map the timing of each step in the patient pathway—from when they had first contact with health services after beginning to experience TB symptoms, received a diagnostic test, to when initiated on TB treatment.

**Results:** Data from 1,604 patients on TB treatment across three countries indicated that 36% first had contact with a health facility within two weeks after symptoms onset. Nearly half received test results confirming TB status within a week of testing; 56% reported initiation on treatment within two days of confirming their status. The results show considerable differences in the pathway from care-seeking to treatment across the three countries. Although patients in Uganda were more likely to experience a delay in having first contact with health-care workers after onset of TB symptoms, a significant proportion of the patients received their test results (85%) and were initiated on treatment (85%) quickly. There were significant delays for patients at each step in care-seeking to treatment in Ethiopia; patients in the Philippines experienced the most significant delays receiving test results. Overall, Ugandans were less likely to have early contact with health facilities to diagnose TB compared with patients in the Philippines and Ethiopia.

Country	First contact with health facility after symptom onset		Received test results to confirm TB status		TB treatment initiated after testing	
	Within 2 weeks	After 2 weeks	Within a week	After a week	Within 2 days	After 2 days
Ethiopia	27%	73%	45%	55%	30%	70%
Philippines	49%	51%	28%	72%	56%	44%
Uganda	30%	70%	85%	15%	85%	15%
Total	36%	64%	49%	51%	56%	44%

[Table 1. Pathway to TB care-seeking and treatment among TB patients in Ethiopia, the Philippines and Uganda]

**Conclusions:** Considerable differences exist among the three measures of pathway to care and treatment of TB; bottlenecks to high-quality TB services vary by country. These results demonstrate the need for a tailored approach to improvement.

### EP13-222-22 Where are the men? A gender analysis of TB cases from targeted community outreaches in South-East and North-East Nigeria

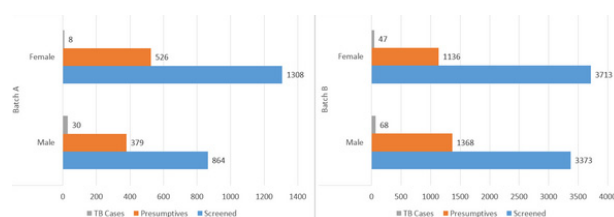
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**Background and challenges to implementation:** Given the significant proportion of missed TB cases in Nigeria, various models of active Community TB case finding interventions have been implemented to complement

health-facility based passive surveillance for TB. In 2019, two batches of WHO supported targeted community outreaches (TCOs) were implemented in Anambra state South-East and Bauchi state North-East Nigeria. The objective of this work is to report the male/female differences in the attendance to and TB cases detected from the community outreaches and highlight the need for specific strategies to target the men.

**Intervention or response:** WHO Nigeria protocol for community outreaches was used to engage selected communities within the participating states. High-level advocacy to community leaders was followed by massive sensitization and awareness creation using existing community structures. Publicity messages were specific for all persons with cough and outreaches lasted between 2-3 days in each community. TCOs were performed in two batches in Anambra and Bauchi states. The second batch of the outreaches adopted strategies specifically targeting men such as massive awareness campaigns in motor parks, artisan markets, and men-only meetings. We report sex-disaggregated data from the outreaches.

**Results/Impact:** A total 9,160 adult community members were screened during the 36 TCOs conducted across the two states. On the whole, women constituted 63% of the total attendees to the outreaches whilst 75% of the 155 total TB cases detected were in Men. As shown in the graph, this differential contribution was consistent during the two batches of outreaches despite a modification in strategy to target men in the second batch.



[Figure. Sex-disaggregated TB data from TCOs]

**Conclusions:** Although the majority of outreach attendees were women, more TB cases were found amongst men. Our findings show that a deliberate modification of the strategy to target men yielded more cases overall. This provides a useful guide for targeted interventions at national and sub-national levels.

### EP13-223-22 Long-term results of surgical treatment of tuberculosis patients

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**Background:** Surgery successfully used in the treatment of tuberculosis (TB), especially when chemotherapy alone does not lead to the desired results. But assessment

of TB surgery (STB) effectiveness faces a number of difficulties, e.g. the formation of a control group, highlighting the effect of surgery on the treatment outcomes.

**Aim of the study:** assessment of STB effectiveness based on data of long-term results of TB patients follow up.

**Design/Methods:** Data of all 18033 TB patients, including 12185 new TB cases (NC), who were registered on standard regimens of TB treatment in 2010-2015 in Moscow, were retrospectively analyzed. For treatment efficacy assessment, proportions of adverse outcomes (AO) within four years of follow up, such as transition to chronic TB forms (CHR), relapses (RL) and TB death (TBD) were evaluated for patients, divided on 2 groups: with STB (858) and other. Given the significant differences in the composition of these groups, multivariable log-regression models for outcomes were calculated, including the factors: STB, treatment history, social-demographics, severity of TB forms, bacteriological and X-ray data.

**Results:** STB decreases the chance of CHR, RL and TBD with OR=0.38 (95% CI 0.27-0.55), 0.48 (0.24-0.97) and 0.40 (0.2-0.82), respectively.

Models showed also, that for NC the chance of these AO is less with OR=0.43 (0.38-0.49), 0.52 (0.43-0.64) and 0.59 (0.5-0.68), respectively; the fact of having a job reduces the chance of CHR and TBD with OR=0.83 (0.73-0.96) and 0.44 (0.35-0.56); bacterial excretion increases the chance of CHR with OR=2.57 (2.25-2.94); caverns in lung increases the chance of CHR and TBD with OR=2.18 (1.92-2.47) and 1.86 (1.6-2.17); age <50 years decreases the chance of CHR and TBD with OR=0.82 (0.72-0.94) and 0.36 (0.3-0.43).

**Conclusions:** The results demonstrate the long-term effectiveness of including STB in the complex of therapeutic measures for TB patients in Moscow.

### EP13-224-22 Patient and health system level barriers to and facilitators for tuberculosis treatment initiation: a qualitative study

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**Background:** The global WHO target is to place at least 90% of all patients diagnosed with tuberculosis (TB) on appropriate treatment. In Uganda, approximately 20% of patients diagnosed with TB are not initiated on TB treatment. We sought to identify the patient and health system level barriers to and facilitators for TB treatment initiation in Uganda.

**Design/Methods:** We conducted focus group discussions with 38 healthcare workers, in-depth interviews with 10 health managers, and 32 TB patients at ten public health facilities (three primary care, four district and three tertiary referral hospitals). Data collection and thematic analysis of transcripts was informed by the Capability, Opportunity, and Motivation behavior change model (COM-B). We identified relevant intervention functions using the Behavior Change Wheel.

**Results:** Common barriers at the health facility level included lack of knowledge about the proportion of patients not initiated on TB treatment (psychological capability); difficulty accessing sputum results due to poor communication between the laboratory and clinic as well as difficulty tracing patients due to inadequate recording of patient addresses (physical opportunity). At the patient level, the notable barriers included long turnaround time for sputum results and lack of transport funds to return to health facilities (physical opportunity); limited TB knowledge (psychological capability) and stigma (social opportunity). The most important facilitators identified at the patient level were quick access to sputum test results either on the date of first visit (same-day diagnosis) or on the date of first return and availability of TB treatment (physical opportunity). We identified education, environmental restructuring and enablement as applicable intervention functions to enhance TB treatment initiation at these health facilities.

Domain	Barriers	Patient Level
Capability	Health Facility Level	
	Psychological	Lack of awareness of the magnitude of pretreatment LPU at the health facilities.
Physical Opportunity	Psychological	
	Physical	Insufficient time and space for patient education Late delivery of sputum samples to the laboratory due to batched sample collection. Lack of tools to monitor TB treatment initiation among patients. Diagnosed with TB Difficulty retrieving sputum test results by most clinics due to lack of collaboration with the laboratory Difficulty tracing patients due to inadequate recording of patient addresses or phone numbers. Disinterest in performing sputum analysis.
Social	Motivation	
	Automatic	Healthcare workers' fear of contracting TB
Reflective Facilitators	Capability	
	Psychological	Mistrust between clinical and laboratory staff
Physical Opportunity	Capability	
	Psychological	Knowledge of QI improvement methods.
Physical Opportunity	Physical	
	Physical	Availability of cough screeners to facilitate TB screening Availability of community healthcare workers to trace patients in the community. Ability to notify patients about their sputum test results through phone calls. Health facility norms e.g. escorting patients diagnosed with TB to the TB clinics.
Social	Motivation	
	Automatic	
Reflective		
	Healthcare workers' sense of duty to the patients	

[Table 1. Barriers and facilitators to TB treatment initiation among patients diagnosed with TB at public hospitals in Uganda]

**Conclusions:** Applying the COM-B model enabled a broad evaluation of barriers to and facilitators for TB treatment initiation at public health facilities in Uganda. The intervention functions identified should be tested for feasibility.

### EP13-225-22 Benefits and harms: the double-edged sword of active tuberculosis case - finding globally, a qualitative study based on expert interviews

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**Background:** Active case-finding (ACF) is a component of the World Health Organization's End Tuberculosis (TB) Strategy. ACF has potential benefits but also potential harms, which need to be carefully balanced when developing and implementing ACF policies. This study aimed to explore experts' views on the benefits and harms of ACF, which can influence the development and implementation of national and global ACF policies.

**Design/Methods:** This was an exploratory qualitative study based on 39 semi-structured TB expert interviews. The experts were affiliated with international, non-governmental and non-profit organizations, funders, government institutions, international societies, think tanks, universities and research institutions. Framework analysis was applied.

**Results:** Perceived benefits included that ACF may reduce patient costs, raise awareness about TB in the community, reach vulnerable populations outside health facilities and reduce TB transmission. These were often linked to the objective of finding and treating TB patients early. Conversely, perceived harms included that ACF may increase stigma and discrimination, cause unintended effects on patients and increase false positive diagnoses and multi-drug resistance. These harms were unintended and often described in contexts where ACF was inappropriately conducted, for example without safeguarding confidentiality.

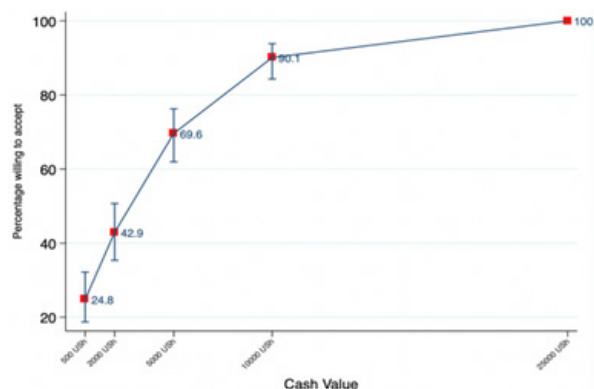
**Conclusions:** These findings provide new insights into the benefits and harms of ACF from international experts' perspectives, highlighting the complex nature of decision making in ACF internationally and locally. This study can help to build a roadmap of benefits and harms to further guide decision-making processes and ACF implementation.

### EP13-226-22 Patient perspectives and willingness to accept incentives for tuberculosis diagnostic evaluation in Uganda

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**Background:** While patient-centered interventions like cash transfers are increasingly recognized as a crucial approach for improving tuberculosis (TB) outcomes, data to support acceptable incentive intervention design that maximizes their utility for improving TB outcomes are limited. We assessed attitudes/perceptions and willingness-to-accept varying incentive structures for completing TB diagnostic evaluation among patients in Uganda.

**Design/Methods:** Between September 2018-March 2019, we surveyed 177 adult patients undergoing TB evaluation at 10 community health centers in Uganda. We collected household sociodemographic information and assessed attitudes/perceptions of incentives. To assess willingness to complete TB diagnostic evaluation in exchange for incentives ranging in value from 500 Ugandan Shillings (USh)-25,000USh (~US\$0.15-6.75), we conducted a willingness-to-accept experiment, which allows refinement of an acceptable incentive value by increasing or decreasing values offered based on respondents' prior answers. We compared associations between willingness-to-accept and patient characteristics using ordered logistic regression.



[Figure 1. Percentage of respondents (N=161\*) willing to accept varying values of incentives in exchange for next-day clinic return. Uganda 2018-2019.

\*161 of 177 participants responded to the WTA component of the survey.]

**Results:** Our sample was diverse by age and gender; median household income was US\$40.05/month (IQR:18.69-80.11). Cash (52%) and transportation vouchers (34%) were the most popular incentive types. Half of respondents preferred unconditional incentives, but for a multi-day evaluation 84% preferred conditioning upon clinic return. Most (90%) accepted \$2.67 (10,000 US\$) as sufficient to motivate next day return for TB diagnostic evaluation.

In multivariate models we found the pairwise difference between the third income quartile and the reference (lowest) income quartile (aOR=2.38, 95% CI:1.20-4.69;  $p=0.01$ ), younger age, and difficulty returning to the health center to be significantly associated with higher minimum accepted incentive values.

**Conclusions:** In Uganda, incentives such as cash or transportation vouchers are an acceptable intervention for facilitating adherence to TB diagnostic evaluation. Household income is associated with preferred incentive structure and value, especially for those at the cusp of the poverty threshold, who are more likely to prefer unconditional/higher valued incentives. Targeted and context-specific socioeconomic supports for at-risk patients are needed to optimize outcomes.

### EP13-227-22 Determinants of delayed diagnosis and treatment of tuberculosis in Cambodia: a mixed-methods study

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**Background:** Cambodia is among the 30 high tuberculosis (TB) burden countries, and approximately 40% of people with TB remain undiagnosed. In this study, we investigated the determinants of delayed diagnosis and treatment of TB in Cambodia.

**Design/Methods:** This mixed-method explanatory sequential study comprised of a retrospective cohort study of 721 people with TB, followed by a series of in-depth interviews was conducted in 12 operational districts in Cambodia. We assessed factors associated with time to TB diagnosis and treatment initiation using Cox proportional hazards model. Subsequently, we purposively selected 31 people with TB based on the time to TB diagnosis, sex, and residence for in-depth interviews. Transcripts were coded, and thematic analyses were performed.

**Results:** The median time from the onset of symptoms to TB diagnosis was 49 days (IQR 21–112). Rural dwellers (aHR 1.25; 95% CI 1.06–1.48); TB symptoms—

cough (aHR 1.52; 95% CI 1.18–1.94), hemoptysis (aHR 1.32; 95% CI 1.07–1.63), and night sweats (aHR 1.24; 95% CI 1.05–1.46); seeking private health care/self-medication (aHR 1.23; 95% CI 1.04–1.45); higher self-stigma (aHR 1.02; 95% CI 1.01–1.03); and education level above the primary level (aHR 0.78; 95% CI 0.62–0.97) were associated with diagnostic delay. The median time from TB diagnosis to the initiation of treatment was 2 days (IQR 1–3). The use of smear microscopy for TB diagnosis (aHR 1.50; 95% CI 1.16–1.95) was associated with treatment delay. Seeking private health care and self-medication before TB diagnosis, lack of perceived risk, threat, and stigma derived qualitatively further explained the quantitative findings.

**Conclusions:** TB diagnostic delay was substantial. Increasing public awareness about TB and consciousness regarding stigma, engaging the private healthcare providers, and tailoring approaches targeting the rural areas could further improve early detection of TB and narrowing the gap of missing cases in Cambodia.

### EP13-228-22 Initiation and management of DR-TB patients as out-patients at a decentralized site shows excellent results thanks to a committed NDOH/NGO partnership in KwaZulu-Natal, South Africa

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**Background and challenges to implementation:** The province of KwaZulu-Natal remains at the epicentre of the HIV and TB epidemic in which King Cetshwayo District notifies over 250 DR-TB cases each year. A specialized MDR-TB unit was responsible for the management of all DR TB patients, requiring clinicians to consult large cohorts of patients who spend up to three days travelling for treatment collection; resulting in loss to follow up (LTFU) rates of up to 15%.

In June 2019, the Ngwelezana hospital TB unit and NGO Médecins Sans Frontières (MSF) launched on-site initiation and management of DR-TB patients residing in the area.

**Intervention or response:** After an initial assessment of readiness of the site early 2019, a five-day training cross-cutting various health care disciplines covered diagnosis, management and adherence for DR-TB. The following six months, National Department of Health (NDOH) and MSF consulted patients together with on-job training as needed; clinical audits showed challenges that were discussed and attended to on multidisciplinary team meetings.

**Results/Impact:** Over a period of seven months, Ngwelezana initiated 47 patients. 53% (25/47) are male; 72% (34/47) co-infected with HIV. Early mortality rates are 4% (2/47) and one patient is LTFU. Five patients (10,6%) required transfer to a treatment centre. 15 patients had positive baseline smear samples and 80% (12/15) converted negative at first month after treatment initiation. More than six disciplines have attended the two multidisciplinary team meetings.

**Conclusions:** Decentralization of DR-TB care and providing ambulatory treatment has been successful with buy-in from on-site staff and through NDOH/NGO partnerships. A formal training followed by on-job support results in correct implementation of guidelines, upskilling of staff and progress monitoring. Motivated health care workers and multidisciplinary meetings result in optimal holistic care for the patient. 90% of patients are now accessing ambulatory treatment closer to home, without any compromise on quality of care.

### EP13-229-22 Reduced nutritional risks and improved dietary pattern among MDR-TB clients enrolled in patient-centered care in Xi'an, Shaanxi province, China

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**Background and challenges to implementation:** High incidence of malnutrition among MDR-TB patients has adverse implications for treatment, including increased disease severity, malabsorption of drugs, delayed sputum conversion, higher mortality, and increased relapse after cure. From January 2019, with support from the FHI 360 Control and Prevention of Tuberculosis (CAP-TB) Project, Xi'an Chest Hospital launched a patient-centered care and counselling model, including nutritional management, to improve MDR-TB treatment outcomes.

**Intervention or response:** The hospital established a nutritional care team including nurses, doctors, MDR-TB counselors and nutritionists. Immediately before and one month after treatment initiation, counsellors conducted one-on-one nutritional assessments using the Nestle Mini Nutritional Assessment (MNA) tool. Counselors and nutritionists provided targeted nutritional education and counselling, including a leaflet on dietary nutrition, as well as monthly small-group thematic sessions for TB/MDR-TB patients that included information on nutrition and healthy diets. At monthly quality control meetings, the care team reviewed cases that needed nutritional support.

**Results/Impact:** From February 2019 to December 2019, 199 MDR-TB patients received nutritional interventions. Chi-square test was used to analyze MNA results. The percentage of patients assessed as well-nourished (MNA score 23-28) increased significantly from 13.1%

at baseline to 57.8% after one month of nutritional intervention ( $P<0.05$ ). The mean MNA score increased from 19.13 to 21.59 ( $P<0.01$ ). The mean scores for patients with severe malnutrition (score  $<17$ ) and malnutrition (score 17~23) increased following interventions, 13.76 vs. 18.88 ( $P<0.05$ ) and 20.13 vs. 22.04 ( $P<0.01$ ), respectively. The following three MNA dimensions showed improved mean scores: anthropometric measurement (1.16 vs. 5.02,  $P<0.01$ ); dietary assessment (1.18 vs. 1.39,  $P<0.01$ ); and subjective global (comprehensive) assessment (0.92 vs. 0.94,  $P<0.05$ ).

**Conclusions:** Nutritional assessment helped detect undernutrition early and identify risk factors requiring intervention. Effective teamwork to deliver targeted education, counselling and support helped MDR-TB patients adopt healthy dietary behavior to improve nutritional status.

### EP14 Reaching the hard-to-reach ones: strategies to overcome the challenges

#### EP14-230-22 Is tuberculosis contact investigation feasible in resource limited settings like Malawi?

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**Background and challenges to implementation:** Tuberculosis (TB) contact investigation contributes to early identification of active TB among close and household contacts of index cases; thus decreasing its severity and reducing transmission of mycobacterium tuberculosis to others. Contact investigation also helps identification of latent TB infection, to allow preventive measures. Implementation of TB contact investigation requires commitment of different units and staffs within the health care setting and community health workers.

**Intervention or response:** In 2015, Malawi national TB programme developed tuberculosis contact investigation standard operating procedures (SoPs). For easy monitoring of the intervention, TB contact investigation registers were also developed. These SoPs and the registers were distributed to health facilities across the country. About 900 health care workers were trained on TB contact investigation and use of the registers. Regular mentorship and supportive supervision were conducted with focus on TB contact investigation. We therefore analysed the implementation of TB contact investigation in Malawi from 2016 to 2019.

**Results/Impact:** The number of contacts registered in contact investigation registers increased by 39% from 16,671 in 2016 to 23,113 in 2019. The number of contacts screened for TB also increased from by 30% from 13,337 in 2016 to 21,231 in 2019. The yield from TB contacts increased from 0.46% (62 TB persons with TB) in 2016 to 0.63% (133 persons with TB) in 2019. The number of under-five children who were started on isoniazid preventive therapy also increased from 2,303 in 2016 to 2,514 in 2019. On the other hand, the treatment completion rate for under five children started on isoniazid preventive therapy was above 90% over the years.

**Conclusions:** Implementation of TB contact investigation is feasible in resource limited settings like Malawi. There has been a great improvement in implementation of TB contact investigation. More needs to be done to increase the yield from TB contact investigation.

### EP14-231-22 Targeted active TB case finding using mobile TB diagnostic units among key affected populations in Malawi, an innovative approach to reach the missing TB cases

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**Background and challenges to implementation:** Malawi misses 50% of TB cases as a result of poor health seeking behavior and limited access to quality diagnostic facilities equipped with tests that have high testing capability. To alleviate this, there is need for an appropriate active case finding (ACF) strategies that are needed to identify and treat these missing TB cases that may not have sought diagnostic services on their own. Screening among high risk population helps to ensure that active TB is identified early to reduce poor treatment outcomes and the risk of TB transmission to the public.

**Intervention or response:** The intervention used seven Mobile Diagnostic Units fitted with digital X-ray configured with Computer aided Diagnosis for TB software (CAD4TB) and a Genexpert platform per truck. Four major cities (Blantyre, Zomba, Mzuzu, Lilongwe) were targeted. Four cardinal signs of TB as well reading radiographs was used to identify presumptive TB cases. The intervention includes, community sensitization by engaging community volunteers, provision of HIV testing services to all TB presumptives cases, symptom and X-ray screening. All clients screened positive for TB underwent Genexpert testing to confirm active TB.

**Results/Impact:** A total of 170,843 clients (Males-99,157; Females-71,686) were screened, 19.2% presumptive TB cases were identified, 1,626 (99.5%) DS-TB cases detected and 7 cases (0.5%) with Rifampicin resistant. Out of the 1,633 TB cases identified, 65% were screened positive on one or more of the four cardinal signs and had an

abnormal CAD4TB score (>60), 35% of TB cases only had abnormal CAD4TB score (>60). The overall yield was high (956/100k) from the total screened.

Quarter	Total screened	Males screened	Females screened	Total presumptive	RR-TB cases	Total TB cases diagnosed	Yield / 100,000
Jan-March 18	1,783	984	799	636	2	8	449
April-June 18	11,150	6,002	5,148	5,409	0	98	879
Jul-Sept 18	20,529	11,285	9,244	5,355	0	131	638
Oct-Dec 18	20,516	11,730	8,786	3,300	1	88	429
Jan-March 19	27,702	14,536	13,166	4,853	0	330	1,191
April-June 19	32,455	21,077	11,378	5,243	1	410	1,263
July-Sept 19	29,284	15,340	13,944	4,312	1	265	905
Oct-Dec 19	27,424	18,203	9,221	3,904	2	303	1105
<b>Grand Total</b>	<b>170,843</b>	<b>99,157</b>	<b>71,686</b>	<b>33,012</b>	<b>7</b>	<b>1,633</b>	<b>956</b>

[Table 1. TB case notification and Yield / 100,000 (March 2018 - December 2019)]

**Conclusions:** Active TB screening remains a priority area that needs more effort in finding missing TB cases. However, targeted screening should be applied at all levels of implementation cycle to improve on yield: by targeting prison, camps (refugee and disaster) and work places within the high burden areas.

### EP14-232-22 Biomedical support to people affected by tuberculosis in prisons, a pilot experience in Cochabamba, Bolivia

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**Background and challenges to implementation:** Bolivia has a WHO estimated Tuberculosis (TB) incidence of 108/100,000 that contrast with 1,073/100,000 TB notification rate in prisons. Although qualified medical staff is available, diagnosis and treatment are hampered by poor adherence to treatment and limited access to biomedical support in prisons. The Regional Tuberculosis Programme (RTP) and Damien Foundation designed a biomedical approach for improving TB-care in prisons in Cochabamba, one of the nine regions of Bolivia.

**Intervention or response:** The Biomedical approach started in 2019 was implemented in all six prisons and included:

1) Training of 70 health promotors among prison-inmates;



- 2) Health-sensitization days where prison-inmates received information about transmission, diagnosis, and treatment of TB provided by health staff;
- 3) Diabetes screening to all presumptive TB cases;
- 4) Daily nutritional supplements for TB cases under treatment;
- 5) Monthly self-help meetings among TB patients under treatment and;
- 6) Tracking system for TB-patients released prisons and still under treatment.

**Results/Impact:** In 2019, there were 186 presumptive patients compared to 236 in 2018. Among them, there were 30 TB bacteriologically-confirmed compared to 19 in 2018. All 30 bacteriologically-confirmed TB were screened for diabetes and none had hyperglycemia. HIV was also tested and there was one HIV-positive. There were 16 patients cured, among them two continued treatment out of prison after being released from prison. There are 14 patients still under treatment. The main issues discussed during self-help meetings were adherence to treatment, fear of not being cured, and the evolution of symptoms.

The main preoccupations of prison inmates during health-sensitization days were TB transmission, clinical presentation of TB, and TB association with other health issues as chronic diseases.

**Conclusions:** The biomedical approach implemented in the prisons of Cochabamba has succeeded to increase the number of TB detected and cured. Peer-support among prison inmates and multidisciplinary collaboration was key for this success.

### EP14-233-22 Barriers to Tuberculosis care among women in selected hard-to-reach areas in southern Nigeria: a mixed method study

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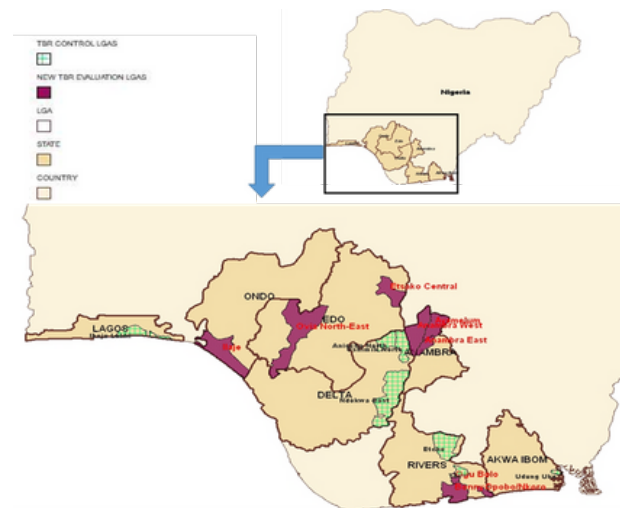
**Background:** Several studies have identified geographical and sociocultural factors as crucial to Tuberculosis (TB) treatment adherence and outcomes. We sought to identify barriers to accessing TB services among women in hard-to-reach communities in a TB REACH Wave-5 Scale-up project implemented by DAHW-German Leprosy and TB Relief Association.

**Design/Methods:** A cross-sectional descriptive study using mixed method approach was conducted among women in 9 hard-to-reach riverine Local Government Areas in 4 purposively selected states in southern Nigeria. Data was collected from 490 respondents using

interviewer-administered questionnaires and 9 Focus group discussions (FDGs) with 81 participants. Outcomes were analyzed using SPSS version-23 and thematic framework.

**Results:** Out of 490 women surveyed, 33.7% (165) aged 25–34 years, 66.3% (325) were married, 45.5% (223) had secondary education and 24.7% (121) unemployed. Furthermore, 45.7% (224) of them earned ≤USD 50 (N18,000) monthly, 62% (304) had 1-4 children. While 11.4% (50) women never heard of TB, 69.4% (340) had poor knowledge of TB. Identified barriers to accessing TB care included stigmatization (269; 54.9%) at health centers, non-involvement in decision-making within the community (217; 44.3%), inadequate health education on TB (183; 37.6%). About 21.2% (104) will not disclose their status if diagnosed with TB, the commonest reasons for non-disclosure being loss of friends (39.4%), business customers (26.9%), and marriage/relationship (21.2%).

Recurrent themes in FDGs were gender prejudice, poor prioritization of women's health and stigma. On stigma, majority associated TB with shame and fear of disrupting relationships; for many, spousal and family disclosure would not even be considered.



[Figure.]

**Conclusions:** Key barriers identified include: low prioritization of women's health, stigma, low TB awareness and poverty in the hard-to-reach riverine communities. Robust gender-sensitive measures such as involving women in decision-making process in the community for TB programmes are highly recommended to address these barriers.

### EP14-234-22 Socioeconomic indicators predict neighborhood-level active case-finding yields better than historic case notification rates in Lima, Peru

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**Background:** A common strategy for targeting TB active case-finding is to identify areas with high TB burdens based on prior case notifications. We assessed the utility of this strategy by comparing historic case notifications with screening yields from a community-based active case-finding program using x-ray vans in Lima, Peru.

**Design/Methods:** We analyzed screening results from Carabayllo District, which we divided into 75 neighborhoods. We calculated screening yield as the percent of screened residents who were diagnosed with TB, by neighborhood. We used binomial logistic regression to assess bivariate associations between neighborhood characteristics and screening yield. Potential neighborhood-level predictors were constructed using the 2017 census and historic TB case notifications. We considered the average TB case notification rate during 2013-2017 (overall and by age and sex), age- and sex- distribution of TB cases, age- and sex- distribution of the neighborhood population, and socioeconomic indicators such as the percentage of households with certain appliances.

**Results:** The x-ray vans screened 29,619 people (13% of the population) and diagnosed 147 TB cases in 12 months during 2019-2020. Historic case notification rate was not significantly associated with screening yield ( $p=0.9436$ ). Neither were neighborhood demographics or demographics of historic TB patients. The percent of households that owned a vehicle was significantly associated; for each 1% of households with a vehicle, we observe a 3% decrease in screening yield (95% confidence interval: 6% decrease-1% decrease,  $p=0.0106$ ). Other socioeconomic indicators with suggestive though non-significant negative associations with screening yield included the percent of households that owned a blender ( $p=0.0717$ ) and the percent that owned a computer ( $p=0.0976$ ).

**Conclusions:** Historic case notification rate was a poor predictor of TB screening yield in these communities, while socioeconomic indicators were better predictors. This suggests that bringing TB screening services to economically disadvantaged communities may help overcome barriers to accessing care.



[Figure.]

### EP14-235-22 Detection of persons with Tuberculosis through innovative engagement of stand-alone private radiology diagnostic centres in Kaduna state Nigeria in 2019

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**Background and challenges to implementation:** Kaduna state has a low treatment coverage with only 22% of the estimated persons with tuberculosis (TB) detected. The missed persons with TB continue to serve as reservoir for continuous transmission within the community. Kaduna state has a sizeable number of stand-alone private radiology diagnostic centers, where clients could walk in or are referred by private/public hospitals for chest X-ray (CXR). The objective of this intervention was to evaluate the contribution of selected private radiology diagnostic centers to TB case detection and how surveillance at these sites could improve TB notification in Kaduna State.

**Intervention or response:** Five highly patronized private diagnostic centres offering CXR services were identified and engaged and available registers were updated to capture full details and contacts of patients, summary report for the CXR and the referring health facility. These data were collected, de-identified and used anonymously. Patients with CXR results suggestive of TB were followed-up for fourteen months (May 2018 – June 2019) through calls, home visits, and visits to the referring health facilities to ensure they were further evaluated using the National TB diagnostic algorithm and placed on treatment.

**Results/Impact:** Of about 4933 CXR conducted, 565 (11.5%) patients had a CXR report suggestive of TB. 303 (54%) of them were further tested with the Xpert MTB/RIF test or evaluated by a medical officer, confirmed to have TB and placed on treatment (74% bacteriologically and 26% clinically diagnosed). The TB surveillance measure instituted contributed 116 (38%) of the 303 TB patients placed on treatment from the engaged private radiology centers. 262(46%) were managed for other respiratory conditions or could not be traced.

Senatorial District	LGA	Radiology facility	No of CXR conducted in the period under review	No. identified	No. placed on Rx without intervention	Additional no. tracked and placed on treatment	No. not treated / managed for other conditions / Could not be traced
Southern	Jema'a	B.M Diagnostics	407	43	18 (42%)	11 (26%)	14 (33%)
Southern	Jema'a	G.Y. Diagnostics	763	85	32 (38%)	18 (21%)	35 (41%)
Central	Kaduna North	First Scan Diagnostics	1568	234	66 (28%)	49 (21%)	119 (51%)
Central	Kaduna North	Dan Musa Diagnostics	1231	127	37 (29%)	21 (%)	69 (54%)
Northern	Sabon Gari	PAL Diagnostics	964	76	34 (45%)	17 (%)	25 (33%)
<b>TOTAL</b>			<b>4933</b>	<b>565</b>	<b>187 (3.3%)</b>	<b>116 (21%)</b>	<b>262 (46%)</b>

[Table.]

**Conclusions:** The engagement of stand-alone private radiology diagnostic centres has huge potential for increasing TB case detection if surveillance at the sites can be improved upon and scaled up nationwide.

### EP14-236-22 Finding the missing cases among high risk populations: lessons from Malawi

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**Background and challenges to implementation:** Active case finding (ACF) strategies are recommended by WHO to identify and treat missing TB cases amongst key populations. The intervention promotes early diagnosis, treatment. Malawi implements active case finding among key populations. Implementation is aimed at identification of the missed cases to improve case detection.

**Intervention or response:** A retrospective programme evaluation of active case finding in Malawi was conducted. 5 districts implemented active case finding from January 2018 to December 2019. Districts conducted targeted screening using, seven mobile diagnostic units (MDUs) equipped with digital X-ray and GeneXpert among key populations. Implementation response included community sensitization (community volunteers), TB screening (symptom & X-ray). TB diagnosis was ascer-

tained by GeneXpert among all positive-screened. Assessment outcome was establishing detection rates of active TB in 24 months post-implementation. Screening data from MDUs was entered into a national TB database. Descriptive analysis used Stata 14.0 (Stata Corporation, Timberland, Tx, USA) for individual records.

**Results/Impact:** A total of 26279 key populations were screened of whom 67% were males. 6492 (24.7%) screened were TB presumptive. Yield of active TB was 4.1% (266/6492) among presumptive TB cases. Cumulative incidence of TB was 1012 per 100 000 people screened (266/ 26279). Incidence of TB (/100 000 people-screened) was 5508 (Internal displaced), 1294 (Refugees), 1128 (HCW), 862(Prisoners), and 784(Miners). 100% (266/266) were initiated on treatment. Yield of TB among presumptives ranged from 1.4%-25.9%. Yield increased by 5.3% (95% CI 0.04-0.07) in 2019 (8.3%, (242/2925) compared to 2018(3.0%, (24/793). High yield of active TB was mainly due to those classified as high burden districts.

**Conclusions:** Targeted screening for TB improves case detection among high risk populations within high burden areas. Scaling up using symptomatic and chest X-ray screening contributes in TB cases notification.

### EP14-237-22 Improving access to TB services for vulnerable populations: an Employer Led Model demonstration in India

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**Background and challenges to implementation:** India's National Strategic Plan identifies over 25 priority or vulnerable populations for TB including miners, factory workers and tea garden workers. Poor working conditions, inadequate ventilation, crowded housing and poor nutritional status amplifies their vulnerability to TB. This is compounded by an overall lack of awareness, limited access to healthcare and the fear of discrimination. There are an estimated 45,000 miners in Odisha and over 6 lakh tea garden workers in Assam. Employers are a viable entry point to accessing these vulnerable populations.

**Intervention or response:** The Employer Led Model (ELM) for TB Care and Prevention was demonstrated in 2 districts of Assam and 5 districts of Odisha. The intervention brought together three stakeholders – district administration, district TB programme and employers. Employers were sensitized on TB through one-to-one or district-level meetings and supported to develop annual action plans. Reporting and recording formats were developed and shared.

**Results/Impact:** Of over 220 companies sensitised, 100 signed Letters of Intent with their respective district and state TB cell. The LOI defined activities and areas of contribution by each partner including active case finding, referral, support during treatment and awareness activities. The time period between sensitization and signing of LOIs ranged from 2 to 8 months. Comprehensive operational guidelines were developed in collaboration with the national TB programme and widely disseminated to aid the implementation process.

**Conclusions:** This intervention has demonstrated a partnership model between employers of populations vulnerable to TB and the NTP to improve awareness of TB and increase access to TB services by integrating TB within the existing structure of establishments. This can potentially be scaled up and replicated in a low-cost manner to other industries in India.

### EP14-238-22 Can mentorship and training improve implementation of TB Infection Prevention and Control in low-resource setting? Malawi experience

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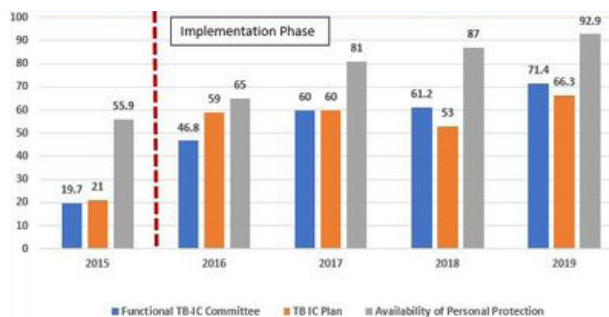
**Background and challenges to implementation:** Implementation of TB Infection Prevention and Control (TB-IPC) in low income countries is a challenge. National TB Programme (NTP) Malawi revised its TB-IPC guidelines to adopt the WHO guidelines for implementation in 2015. Various intervention including training and mentorship were organized at country level. An implementation evaluation was conducted to compare key TB-IPC indicators pre and during the intervention period.

**Intervention or response:** In 2016 trainings and on-site mentorship were organised targeting high and medium volume TB registration facilities. An evaluation of before and during intervention of all facilities implementing a TB-IPC was conducted. Facilities implementing TB-IPC between Jan-Dec 2016-2019 receiving initial training and followed by quarterly on-site mentorship from NTP were included and assessed. Data collection methods used: supervisory checklist; administration of questionnaires with TB-IPC focal persons and key staff. Assessment objective was to determine functionality of TB IPC committees, availability of TB-IPC plan, and availability of personal protective equipment (PPE) in Malawi. Outcome was to establish impact of onsite-mentorship and training as an intervention for TB Infection Prevention and Control.

**Results/Impact:** By 2019, a total of 392 facilities were trained and mentored. From 2015-2019, facilities reported as “established and functional TB IPC committees” ranged from 19.7%- 71.4%. A total of 260 (66.3%) fa-

cilities reported availability of a TB infection plan in 2019 from 21% in 2015 Availability of PPE ranged from 55.9% - 92.9% between 2015-2019.

**Conclusions:** The initial training followed by regular on-site mentorship improved TB-IPC system in low resource settings. Strengthening on-site mentorship and training in Malawi is of crucial importance in TB IPC. Onsite mentorship is also cost effective in low income countries like Malawi.



[Figure 1. Performance trend on TB infection prevention and control measures in Malawi]

### EP15 All hands on deck: key stakeholders take initiative to end TB

#### EP15-239-22 School-children as TB-Ambassadors played crucial-role to fight TB-epidemic by disseminating messages-of symptoms & free treatment among their peers, family members and neighbourhood in five-NTP-districts, Odisha

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**Background and challenges to implementation:** Tuberculosis is curable-and-preventable, and yet it-remains-one-of-the-greatest-threats-to-health-globally. TB has a notorious-track-record as a ‘Captain-of-the-Men-of-Death’ that kills 4,000 people-each-day, and 1.5 million-people-each-year. TB is the-leading-killer of people-living-with-HIV/AIDS. An estimated 10 million-people-developed-TB in 2018, and nearly-half-a-million-people-developed drug-resistant-TB. An untreated-active-TB-patient infects-around 10 to 15 people-annually. In spite-of complete-geographic-coverage of NTP-in-India, many-TB-suspects remain-undiagnosed.

Realizing the-value-of-school-children in-community-mobilization, five-NTP-districts in-Odisha engaged-them in tuberculosis-control-activities. A school-based-intervention was designed to-sensitize and groom-students as "TB-Soldiers"-(TBS). We evaluated the-intervention and success-achieved in-these-five-districts as a-pilot which-was later-replicated elsewhere.

**Intervention or response:** Envisioning to involve the-school-children, studying in 6th-10th standards, as ambassadors/messengers of TB in spreading-awareness about the-disease among their peers'/class-mates, school, home and the-community as-a-whole was planned in 5 of 31 target-NTP-districts in-Odisha. Key-messages on causative-agent of tuberculosis, modes-of-transmission, environmental-factors, identification/diagnosis/complete-cure, free-treatment availability, location & meaning of DOTS, duration-of-treatment, prevention and vaccine-for-tuberculosis were delivered during-various-sessions. Children were groomed-as-TBS through a well-structured communication-protocol. Trained Community-Volunteers of local NGOs and Healthcare-Workers informed the sub-district level-supervisors about TB-symptomatic as reported-by-the-children. The awareness aimed-to-enhance TB-case-detection & treatment-success-rates in the-targeted-communities/areas.

**Results/Impact:** Participation was 100% among the 250 target-schools as intervened. 7,650 students were-sensitized through 1,250 sessions. 347symptomatic-cases as-identified thru 54-designated-microscopy-centres by the-TBS were reported-to the-CVs/HWs at the school level. All 37 patients (29 thru-sputum and 8 thru-CXR) as-diagnosed were put-on-treatment. Around 2/5th cases were-detected from-their-neighbourhood. Specificity in case-identification was around 40%. Most symptomatic-cases were reported by-students-of 8th-10th standards. 20% cases were reported on-the-same-day, while 40% each were-reported within 2-7 days-of-the intervention.

Total no. of schools in the district	No. of schools involved	No. of school children involved	Population educated about TB disease/program	No. of diagnostic/treatment centers engaged	Total referrals for sputum exam done	Total Patients diagnosed as TB (sputum test+CXR)	Diagnosed TB patients put on DOTS
1975	250	7650	100000	54	347	29 + 8 = 37	37

[Table 1. Intervention details of School Activity in five districts in Odisha during 2019]

**Conclusions:** 37 lives were saved with around 1 lakh people educated about TB-disease and the NTP. This planned low-cost-unique model for TB-control-attempt by using the school-students as a medium for-community-mobilization proved as highly-effective-strategy to diagnose-TB-patients.

Although not fully-utilized, sensitizing and engaging school-children as-TBS has immense-potential to-reach-out-to the contact-cases and increased-awareness among

the peers/target/unreached-community. However, further evidence-based-studies are recommended for larger and effective engagement of the TBS.

### EP15-240-22 Under-five TB case finding in hard to reach areas - a case for Malawi

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**Background and challenges to implementation:** Integrated community case management (iCCM) was developed in 2000s by WHO and UNICEF in collaboration with other partners to bring treatment services 'closer to home'. In 2008, Malawi trained an existing cadre of Community Based Health Workers, known as Health Surveillance Assistants (HSAs), to provide integrated community case management of childhood illness in village clinics. These HSAs come in contact with sick children with a number of diseases which are often present in the same individual and have overlapping clinical signs. Screening under-five children for Tuberculosis at first contact has two advantages. The first one is to identify contacts with undiagnosed TB disease among the contacts of an index case, and second, to provide preventive therapy for contacts without TB disease but are susceptible to developing disease following recent infection.

In Malawi, 30–35% of the population lives more than 8 km from a health center and there was no integration of under-five TB interventions in IMCI strategy.

**Intervention or response:** From 2016, IMCI and NTP extended integration of management of childhood illnesses to Tuberculosis. HSAs identify under-five contacts to pulmonary tuberculosis cases and refer them to health facilities for further management. Update of IMCI tools (manual and sick child recording forms) to accommodate Tuberculosis took place in 2017. From 2018, with funding from World Bank, a total of 144 CCM providers drawn from four districts were trained in TB case detection.

**Results/Impact:** A total of 1,909 under-five children were assessed from 48 village clinics in 2 districts (Balaka and Nsanje) and 3.1% (60) were referred to nearest health facilities for IPT initiation and further examination.

**Conclusions:** Village clinic providers contributed to initiation of under-five contacts to TB patients in hard to reach areas. This entails the need for continuous integration of TB in IMCI.



### EP15-241-22 Caregivers' beliefs in anti-tuberculosis medicines in the African/Indian SHINE trial

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**Background:** Adherence to anti-TB treatment (ATT) remains an unresolved challenge in treating paediatric tuberculosis. To better understand barriers to adherence, we explored beliefs in medicines among the carers of children on ATT in the SHINE trial in India, South Africa, Uganda, and Zambia.

**Design/Methods:** This was a substudy of the randomised ATT shortening SHINE trial, including 1206 children aged 0-16 with smear negative minimal TB. We used a modified version of the validated 18-item, 5-point Likert-scale Belief in Medicines Questionnaire (BMQ) to measure carers' beliefs in medicine in general as well as beliefs about ATT. Scores for questions relating to the same factor were combined to create a total score for each participant for four factors: necessity, concern, overuse, and harm. Necessity and concern factors were related to ATT treatment, and overuse and harm factors were related to general medicine. The scale allowed for scores to range from 5 to 25 on each factor with a higher mean indicating greater strength of belief. We compared beliefs at baseline, 8 weeks, and end of treatment, using a paired t test.

**Results:** 1204 carers completed a questionnaire at one or more time points. Median child age (~1:1 sex ratio) was 4.04 years (IQR: 1.74 – 7.98). There was a significant change over time in the paired scores per participant, between baseline and the end of treatment visits. Necessity scores increased from 15.19 to 15.97 ( $p < 0.00$ ), concern scores decreased from 13.08 to 10.59 ( $p < 0.00$ ), overuse scores decreased from 10.36 to 9.86 ( $p < 0.00$ ), and harm scores decreased from 8.26 to 7.24 ( $p < 0.00$ ).

**Conclusions:** Overall, caregivers reported positive belief in ATT and low negative beliefs about medicine in general. The results are encouraging that with adequate education, health beliefs will not unduly hinder implementation of improved treatments in high burden contexts.

### EP15-242-22 Active Tuberculosis case finding in refugee camps, a right for all

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**Background and challenges to implementation:** Refugees are at high risk of developing TB with limited services provided specifically in their camps. However, the coexistent of illnesses and poor nutritional status of many refugees weaken their immunity and make them more vulnerable to develop Tuberculosis (TB). Furthermore, overcrowding living conditions have the potential to facilitate TB transmission.

Malawi has become not only important transit country for immigrants but also preferred choice of destination. Immigrants to Malawi originate from Mozambique, DRC and Burundi. Currently 40,000 refugees are at Dzaleka refugee camp in Dowa district.

Dzaleka camp clinic provides health services free of charge. However, there is shortage of staff at the clinic and this prompted the Malawi NTP to engage volunteers.

**Intervention or response:** To mitigate the challenge, from July, 2019, NTP with support from World Bank trained 30 volunteers from the camp to build their capacity on TB issues. During the four days, their roles such as day to day TB screening and health education to cope stigma issues were outlined. Reporting tools and enablers like N95 masks for infection prevention were provided after the training.

**Results/Impact:** Findings have shown that volunteers have contributed to TB case finding. Over a period of nine months' period (July, 2019 to March, 2020). A total of 90 presumptive TB cases were identified and out of those 4 TB cases were diagnosed ( $M = 2$ ,  $F = 2$ ) through microscopy. This presented a positivity rate of 4.4%. All the TB cases were initiated on treatment.

**Conclusions:** Volunteers in refugee camps have contributed to TB case detection effort in the district. This entails the need for continuous involvement of volunteers in all camps in the country. Furthermore, provision of infection control supplies like masks, hand washing soap have proven to motivate them.

### EP15-243-22 Community volunteers: what motivates them to be part of the TB world?

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**Background and challenges to implementation:** Empowering people with TB and their communities through partnerships, social mobilization, advocacy and communication strategies and promoting the implementation of patients' charter are key components of the Stop TB Strategy. Community-based TB activities cover wide range of activities contributing to prevention, diagnosis and improved treatment adherence. Until 2016, implementation and scaling-up of community-based TB activities remained weak in Malawi despite clear need and documented cost-effectiveness of these activities.

**Intervention or response:** In 2017, Malawi National TB Programme (NTP), with support from Southern-Africa Tuberculosis and Health Systems Support Project revamped community-based TB activities in 9 districts. World Health Organisation's guidelines for community engagement in TB activities were adapted. Community members chose community-based volunteers to form committees with an average of 10 members per committee. NTP trained volunteers for 5 days. Main roles of committee members were awareness creation, advocacy, sputum collection and transportation, TB screening among others. Enablers like push-bikes, gumboots, raincoats, T-shirts, bags, umbrellas, gloves, N95 masks, were provided. Six-monthly support supervisory visits to volunteer-committees were instituted. We, therefore, analysed the drop-out rate of these volunteers, reasons for dropping out and their needs.

**Results/Impact:** A total of 658 volunteers were trained; 348(53%) males and 310(47%) females. By February 2020, 59(10%) males and 54(8%) females had dropped out. Of the 113 volunteers who dropped out, almost 50% dropped because their expectations were not met, 12(11%) migrated to South Africa, 6(5%); all females) dropped-out because of family issues. A good number of volunteers also dropped out for unknown reasons. Volunteers mainly mentioned refresher trainings, availability of enablers and support supervision by health workers as main issues that the NTP should address.

**Conclusions:** Community-based volunteers can still be sustained in resource-limited settings like Malawi. Volunteer selection and clear job description are very critical. The NTP needs to put in place measures to sustain the already trained volunteers.

### EP15-244-22 Role of community health workers in patient-centered care for TB

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**Background and challenges to implementation:** BRAC has been implementing TB control programme in Bangladesh over more than 20 years in collaboration with the National TB Control Programme BRAC is a non-governmental organization (NGO) and its TB control programme aims to reach every corner of the country for accessing services easier for the community people. Currently, it is serving 101 million populations with more than 60,000 community providers with the support of the National TB Control Programme.

**Intervention or response:** BRAC's frontline health workers known as Shasthya Shebika (SS) play an important role in implementing community interventions. They receive training from BRAC on the treatment of common illnesses including basic information on tuberculosis. They disseminate TB messages in the community during household visits and group meetings, identified TB presumptive, and refer them to the NTP designated facilities for diagnosis. After diagnosis TB patients are referred to the community back and their daily DOT is ensured by nearby SS. The factors responsible for success, the involvement of SSs, the bond money obligation, out-reach programme, free drugs, and availability of technical and financial resources.

**Results/Impact:** Sustained improved treatment success rate over the decade is more than 92% is the evidence of effectiveness of the BRAC community-based programme and the DOTS approach. Service intensification result three times increased TB case notifications of all form from 95,760 to 291,595 and pulmonary positive 71,946 to 162,195 from 2009 to 2019 respectively. Among the total cases identified in 2019, BRAC's community health workers contributed 38%. The rate of MDR-TB among new patients is also relatively low, 1.5 % due to the successful implementation of the DOTS strategy by SS.

**Conclusions:** Intensifying community-based TB services through community health workers showed better results in increased case notification, to maintain high treatment success rate and DOTS expansion through patient-centered approach, and easy to introduce any potential interventions successfully.



### EP15-245-22 Addressing diagnosis delay in tuberculosis (TB) patients through engagement of Lady Health Workers (LHWs) in Pakistan

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**Background:** TB is one of the major public health problems in Pakistan. Due to high incidence of upper respiratory infections with overlapping symptoms particularly productive cough, delay in diagnosis of TB is quite common. The present study is an attempt to address the diagnosis delay in TB patients through involvement of LHWs who are front line community health workers in the country.

**Design/Methods:** This cross sectional study was part of a pilot project implemented by Mercy Corps in three rural districts of Sindh Province. Since there is no standard cut off point to calculate the delay in diagnosis in days; early diagnosis is demonstrated through comparison of data between the beneficiaries of the PPM project and the LHW pilot Project.

A cohort of 242 persons with bacteriologically confirmed TB (registered during January – March 2018) was considered as the total population for this study, including 145 persons with TB diagnosed through LHW pilot intervention and 97 from the PPM intervention.

Through systematic random sampling patients were selected from intervention-wise patient register. Patients were contacted telephonically to gain informed consent. Face-to-face interviews were administered by using validated data collection tool to measure diagnosis and treatment delay.

**Results:** The results showed that the average number of days between onset of symptoms and diagnosis of TB were 119 in case of patients registered through PPM while it was 72 days in case of LHW intervention. This shows that through LHW intervention, people with TB signs or symptoms were diagnosed 47 days earlier as compared to patients diagnosed through PPM.

**Conclusions:** The study demonstrated that the engagement of LHWs can significantly reduce the delay in diagnosis of TB patients.

### EP15-246-22 The road mapping of the community contribution in the battle to End TB in Senegal

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**Background and challenges to implementation:** In Senegal, the participation of community-based organization (CBO) in the fight against TB was not effective until 2012, and is related to the Global Funds recommendation with two components: technical and community led by Plan International Senegal. Since then, the community's contribution to TB detection and treatment success rates has continued to improve, placing this strategy at the heart of disease control and sentinel population in the search for missing cases and the achievement of End TB goals.

**Intervention or response:** This is an analysis of the global reporting data for confirmed tuberculosis referred by community workers from 2013 to 2019, compared to the total cases reported in the country. This was followed by a comparison of the treatment success rate of patients followed-up by CBOs with that of the country.

**Results/Impact:** In 2013, the CBOs detected 1,182 teste positive pulmonary tuberculosis out of 10,658 suspected oriented cases, representing a positivity rate of 11%, while in 2019 for almost the same number of suspected oriented cases (12815), 2,525 cases of positive pulmonary tuberculosis were detected which represent 20%. The number of cases of TPB referred by the community increased by 53%, while the community contribution on the country's total PBTs rose from 11% in 2013 to 21% in 2019, an increase of 10 points in 6 years.

The success rate for the treatment of cases entrusted to CBOs has increased from 88% in 2013 to 95% in 2019 for a national average of 86%.

**Conclusions:** Analysis of these results shows that over the past 6 years the fight against TB in Senegal has been strengthened by an increasingly efficient Community system characterized by a continuous improvement in the quality of services delivered. It also shows that community involvement could be one of the most accessible solutions to end TB.

### EP15-247-22 Engaging dairy cooperatives to support TB patients: a pilot from rural Bihar, India

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**Background and challenges to implementation:** Community engagement is pivotal to an adequate TB response at the grassroots. Promoting the participation of citizens should be central to it. The community can participate in supporting patients and their families and health workers. Active community institutions like dairy cooperatives can be a suitable forum for it.

**Intervention or response:** We piloted a program to involve dairy cooperatives in TB response from September 2015 to December 2017 in 360,000 of Samastipur district of Bihar, India. We engaged with 15 cooperatives with about 2250 total members. In addition to sensitizing the members on TB symptoms and its social determinants, the objective was to seek daily milk donation directly to the TB patients on treatment in their area. The engagement process involved 2-3 meetings per month with cooperatives, coordinating with TB patients, and reporting the progress to the cooperative officials. From a list of all the patients in their area, cooperative members decided whom to support and for how long based on their understanding of the patient's socioeconomic status. The cooperatives used their social welfare fund (10% of their annual profit) for the donations.

**Results/Impact:** Out of the 244 patients for whom support was sought, 126 (52%) patients on treatment were supported by the cooperatives. About 48% of the patients were female. Out of 792 patient-months of treatment, patients received nutrition for 58% (461) of patient-months. About 68% (86) patients received 250ml milk daily, and 32% (40) received 500ml milk daily during the period of support. Members referred other presumptive patients to health facilities and ensured adherence for patients they supported.

**Conclusions:** Community institutions can be a vehicle for engaging citizens. In addition to building an understanding of TB, these community structures can complement social security schemes for TB patients.

### EP15-248-22 Stakeholders perceptions on the ethics, transparency, and fairness of clustered trial randomisation

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**Background and challenges to implementation:** Cluster randomized trials have gained popularity in public health research. However, there is little published research on stakeholder perceptions of the ethics, transparency, and fairness of randomization. We sought to assess comprehension of trial procedures and satisfaction with the randomization process.

**Intervention or response:** The GeneXpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) trial is a cluster-randomized trial of onsite GeneXpert testing at 20 community health centers in Uganda. We conducted cluster randomization at a public randomization ceremony to cultivate stakeholder engagement and increase trust in the randomization process. Following the ceremony, we administered a survey comprised of seven questions on a 5-point Likert scale.

Variables	Survey Responses (N=54)	
	n (%) with score >=4	Median (IQR)
Understand goals and design of trial	54 (100%)	5 (4-5)
Believe trial is relevant national goals for improved TB care	54 (100%)	5 (5-5)
Understand randomization and its importance	52 (98%)*	5 (4-5)
Believe randomization process was fair	52 (96%)	5 (5-5)
Satisfaction with randomization outcome	52 (96%)	5 (5-5)
Believe it was important to participate and witness randomization process	54 (100%)	5 (5-5)
Believe attendance at randomization will help other colleagues accept randomization outcomes	53 (98%)	5 (5-5)

[Table 1]

**Results/Impact:** The ceremony began with the Acting Assistant Commissioner from the Uganda National Tuberculosis and Leprosy Programme (NTLP) introducing the trial in the context of TB diagnosis in Uganda. Trial investigators then gave brief presentations on the trial design and randomization procedures. After questions were answered, randomization was conducted as a two-step process with active participation from stakeholders. Site representatives from four sites randomly selected one

football each from an opaque bag containing ten footballs labeled with a number between 0 and 9, which was used to select a random allocation sequence linked to stratified/restriction group assignment. An impartial NTL representative then randomly selected a numbered football from the same bag, which determined which group received the intervention. Survey responses were positive, with high comprehension of randomization (98%), trust in the randomization process (96%), and satisfaction with randomization outcomes (96%) (Table 1).

**Conclusions:** Public randomization ceremonies should be considered in community-based randomized trials to increase engagement of trial stakeholders.

### EP15-249-22 Tribal Action Plan Fund Utilisation under National Tuberculosis Elimination Program: how does Chhattisgarh state in India fare to improve program performance?

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**Background and challenges to implementation:** India reports more than 25 lakh active tuberculosis patients and more than four lakh TB deaths every year by remaining as a major public health problem particularly amongst the tribal population in India. Poor physical access to diagnosis and treatment under NTP still remains as a problem for this disadvantaged group who generally reside in hilly and difficult to reach areas. The availability and utilisation of health care services remains a challenge; demand side barriers, structural constraints, human resource issues and the provider attitudes are particularly acute in the tribal areas.

NTP implements Tribal Action Plan (TAP) for tribal areas/populations on priority basis as “special populations and hard to reach” groups for service delivery and has made several special norms and guidelines for better implementation for the designated areas/populations. Despite its implementation since 2005; the tribal communities continue to face multiple challenges including access to TB diagnostic and treatment services.

We conducted this study to determine the trends of financial utilisation for the special provisions available under the TAP like:

- (i) patient honorarium (PH),
- (ii) incentive for sputum collection and transport (ISCT),
- (iii) incentive for programme staff (IPS) and;
- (iv) incentive for vehicle maintenance (IVM).

**Intervention or response:** A cross sectional study based on mixed method approach was conducted in 13 TAP implementing districts in Chhattisgarh, during Nov’16 to Jun’17 that included review of RNTCP financial records and reports at the State TB Office and District TB Centres. District TB Officers, TB Unit Supervisors and Block Medical Officers implementing TAP were interviewed by using a semi structured questionnaire to ascertain and analyse the trends of TAP fund utilization.

Three key variables;

- (a) Budget estimated in PIP by the districts,
- (b) Budget approved by National Health Mission to the districts, and;
- (c) Budget utilized by the districts were included for the above said four activities of PH, ISCT, IPS, and, IVM.

Retrospective financial data for five financial years from the 13 TAP implementing districts for 2012-13 to 2016-17 was collected, compiled and analysed. The data was collected electronically thru Microsoft excel sheet and their percentages/proportions calculated by using Epi-Data version 2.2.2.183 for analysis (EpiData Association, Odense, Denmark). Ethics approval was obtained from The Union Ethics Advisory Group, Paris, France while the administrative approval for conducting the study was obtained from the NTP State TB Cell, Chhattisgarh.

**Results/Impact:** Overall, the trends on states expenditure on tribal action plan in terms of absolute numbers has increased over the five years period; however, in terms of fund utilization against received ranged from 37-86% with the utilization rate less than 44% in the recent years. Utilization rate under Patient Honorarium is  $\leq 33\%$ , Sputum Collection & Transport  $\leq 37\%$ , Staff Incentive  $\leq 56\%$ , and  $\leq 48\%$  under Vehicle maintenance. Low utilization was due to scarcity of funds, procedural delays and tribal areas affected by insurgency/Left Wing Extremism.

Financial Year	Patient Honorarium		Sputum Collection & Transport		Staff Incentive		Vehicle Maintenance		State
	INR (in Millions)	Proportion of Expenditure	INR (in Millions)	Proportion of Expenditure	INR (in Millions)	Proportion of Expenditure	INR (in Millions)	Proportion of Expenditure	INR (in Millions) / Proportion of Expenditure
2012-13	0.6	50%	0.2	NA	0.9	75%	0.3	100%	1.8 / 86%
2013-14	0.6	60%	0.4	80%	1.6	76%	0.5	100%	3.0 / 73%
2014-15	0.8	27%	0.3	19%	1.6	54%	1.9	48%	4.7 / 40%
2015-16	1.1	33%	0.4	31%	1.8	56%	1.9	48%	5.2 / 44%
2016-17	1.1	25%	0.6	37%	1.4	50%	1.0	28%	10.7 / 37%

[Table 1. Absolute figures for utilization and the proportion of expenditure for different components of Tribal Action Plan, Chhattisgarh, India]

**Conclusions:** The strength of this study is that the figures are derived from documents of the actual activities conducted which otherwise is not publicly available and reflects the ground realities under programmatic conditions. However, the limitation is that the study is from 13 districts of Chhattisgarh and the findings cannot be generalised to other field settings elsewhere in the country. Further research is needed to ascertain the process related issues in these settings and areas.

The trend of utilisation of TAP is less than 50% over the recent years. There is an urgent need for the administrators to intervene and improve the efficiency of fund utilisation at State and district levels. This is a worrisome factor for the programme as the envisioned health care services are not being efficiently delivered to the tribal population and calls for immediate attention of the administrators/Program Managers to streamline the financial management.

### EP15-250-22 Tuberculosis, in the shadow of Covid: Indian media's coverage of TB during the Covid-19 pandemic

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**Background:** Media plays a crucial role in setting the public health agenda by raising public awareness and building discourses that can make or break governments' policy implementation. A brief evaluation was done to assess if the overwhelming media preoccupation with COVID drew attention away from TB- a programme which desperately needs greater public attention and support to succeed.

**Design/Methods:** To qualitatively analyse the coverage of tuberculosis by Indian media, two leading news dailies in English and Hindi were selected based on the Audit Bureau of Circulations. All articles on TB between January to April 2020 were selected, Comparisons were primarily made across

- Time (January-February vs March-April),
- Type of Media
- Language
- Themes, to document change of discourse, if any, after the Covid-19 pandemic set in.

Articles were also taken through specific keyword searches in online news media. Thematic analysis was done using Weft-QDA software.

**Results:** During January-February 2020, TB was focussed in 82 reports in selected leading English and Hindi dailies, covering themes including case finding, local programmatic issues, and newer modalities of management. Reportage decreased by about 34% in the selected dailies, during March-April 2020 corresponding with increasing Covid patients and the accompanying lockdown in India. Coverage now focussed on the role of BCG vaccine against Covid, use of TB diagnostics and

facilities for Covid management. Online news channels adopted a health systems' lens, highlighting systemic weaknesses in adequately responding to the dual crisis of TB and COVID.

**Conclusions:** Indian media's coverage of TB contributes significantly to increasing public awareness. Issues around the Covid pandemic were leveraged more by online news media than print media, to draw attention towards TB- implying that the deeper public penetration of print media is insufficiently tapped. A more detailed analysis of daily newspapers in other Indian languages can help to find areas which need more coverage.

### EP16 TB: new insights on cost and cost-effectiveness

#### EP16-251-22 Standardized framework for evaluating the cost-effectiveness of tuberculosis (TB) case-finding and treatment initiation projects

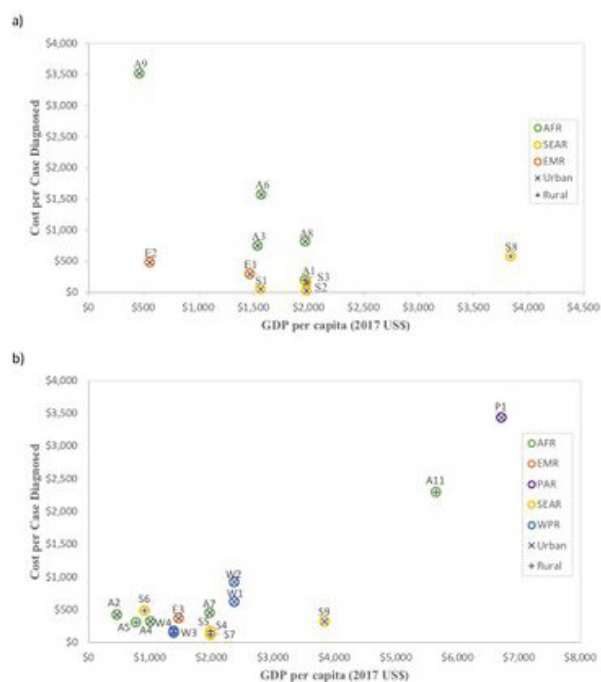
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**Background:** Interventions that can help streamline and reduce gaps in the tuberculosis (TB) care cascade can play crucial roles in TB control efforts. Such interventions are often operationally complex and resource intensive, and there is a need to better understand their value to support decisions for future funding, strategic adoption and program scale-up.

**Design/Methods:** We comprehensively reviewed TB REACH Wave 5 program reports and financial statements. Two independent reviewers abstracted cost (in 2017 US dollars) and key programmatic data, including project type ('case-finding only' or 'case-finding and treatment'), operational settings (urban vs. rural), and project outputs (numbers of people with TB diagnosed by the project, started on treatment, and successfully completing treatment). Cost-effectiveness for each program output was calculated as the ratio of apportioned programmatic costs and respective service output estimates.

**Results:** Of 28 eligible projects, 12 were exclusively case-finding, 16 further included treatment support in addition to case-finding. Most projects were implemented in the African or South-East Asia, and 19 focused on serving urban areas. Average program cost per case diagnosed across all projects was \$221, which was higher for projects with objectives beyond case-finding and in-

creased with per-capita GDP. For projects conducting activities beyond case-finding, the average cost per treatment initiation was \$353 and per treatment completion was \$738.



[Figure 1. Cost-effectiveness (cost in 2017 US dollars per case diagnosed) of TB REACH Wave 5 projects focused on a) case-finding only and b) case-finding and treatment support, by geographic region and setting.]

**Conclusions:** Our work demonstrates that costs and cost-effectiveness of TB case finding are highly context-specific and dependent on programmatic objectives. Costs were generally higher in areas with greater economic development. Our analytic framework can be extended to evaluate a variety of other activities, thereby improving comparability, monitoring, and evaluation of programs designed to improve the TB care cascade.

## EP16-252-22 Interferon gamma release assay is a cost effective option for provision of tuberculosis preventive therapy in high burden resource limited settings

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**Background:** Interferon gamma release assay (IGRA) is recommended by the World Health Organization for diagnosis of latent tuberculosis infection (LTBI). However, its utility in resource limited settings has been limited by concerns about cost. This cost effectiveness evaluation was part of a feasibility study on the implementation of IGRA in Uganda.

**Design/Methods:** Costs associated with provision of Tuberculosis Preventive Therapy (TPT) following IGRA or symptom based screening were derived from; salaries, training, transport, laboratory, three-month isoniazid-rifapentine (3HP) and adherence support costs from the Ministry of Health. The national health system perspective and a two-year time horizon were used because TPT effectiveness wanes after 2 years. The TPT cure rate, TPT completion rate, and IGRA positive predictive value for developing active TB used were; 40%, 73% and 2.7% respectively. Outcomes included; cost per TB case and TB infection averted, and cost per quality of life years (QALYs) gained from averted TB. Univariate sensitivity analysis was performed using excel with parameters varied by +/-10%.

**Results:** Costs for IGRA and symptom screen based TPT provision were US\$ 183,140 and US\$51,851 respectively. The incremental cost was US\$ 131,289 while IGRA and symptom screen cost effectiveness were US\$ 15,520 and US\$1,440, respectively. QALYs gained for IGRA and symptom screen were 11.6 and 36 respectively. The incremental cost effectiveness ratio (ICER) for QALYs gained, TB disease and TB infection averted were US\$ -1,687.5, US\$ 2,854 and US\$ 2,819, respectively. ICERs were sensitive to changes in transport and salary costs but stable to changes in IGRA, laboratory, and 3HP costs.

**Conclusions:** IGRA based TPT is cost effective for TB disease and TB infections averted, and therefore a viable option for TPT provision in resource limited settings.

### EP16-253-22 Pre-treatment costs for TB patients – results from an observational cohort study in Johannesburg, South Africa

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**Background:** In South Africa both diagnosis and treatment of TB are free of charge for the patient, but patients still incur substantial costs accessing health services. We describe the direct (out-of-pocket) payment that patients incur before TB treatment initiation.

**Design/Methods:** Ongoing observational TB cohort study among adult patients in Johannesburg receiving treatment for pulmonary TB through the South African national TB program. Patients with drug-susceptible TB were recruited at TB treatment initiation between 09/2017-01/2020 and administered the WHO TB Patient Cost Survey. The survey captured both medical and non-medical costs. We report median (interquartile range, IQR) pre-treatment costs of TB per patient from the patient perspective, stratified by provider type, in 2018 USD.

**Results:** 329 patients were included in the analysis. The median direct cost incurred per patient before treatment initiation was \$3.79 (IQR:0.74-11.76). For medical costs (62% of the total), the largest expense was consultation (47%), followed by medication (36%), laboratory fees (8%), and procedures (5%). For non-medical costs (38% of the total), the largest patient-expense was transportation (70%). Before treatment initiation, 69%, 22%, and 6% of patients visited 1, 2, or  $\geq 3$  health-care providers, respectively. Pre-treatment costs increased from a median of \$3.35 at the first provider to \$4.17 at the second, with pharmacy (11%, median \$16.37) and private practitioners (10%, median \$37.20) substantially increasing out of pocket payments compared to public care (76%, median \$0). A third of patients (31%) reported a moderate to very serious financial impact of TB; 7% used their savings while 4% borrowed money to help pay for pre-treatment expenses.

**Conclusions:** Even before starting TB treatment, South African patients incur costs equivalent to approximately 3 hours minimum wage. Total TB care costs should include pre-treatment costs as these contribute to the economic burden of TB on the patient and their household.

### EP16-254-22 The costs of providing TB services in healthcare facilities in Kenya: a case for investment to end TB

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**Background:** Reducing Kenya's TB burden can be achieved through bridging the substantial resource gap by improving resource allocation to and within the National TB, Leprosy and Lung Disease Program (NTLD-P). This study aimed to estimate the unit costs of a comprehensive set of TB services and develop a sustainable cost data collection framework for the NTLD-P.

**Design/Methods:** We estimated the costs of all the TB interventions in Kenya in a representative sample of 20 public and private health facilities from eight counties. The unit costs estimated from a health provider's perspective were calculated using bottom-up (BU) and top-down (TD) approaches for the financial year 2017/2018. We analyzed the cost data using MS Excel and STATA 16 and calculated the average measures at national level. Univariate sensitivity analyses were performed on elements such as utilization to assess the robustness of the results.

**Results:** The BU unit cost of passive case finding (PCF) averaged for all facilities was found to be US\$29 and US\$30 for pulmonary TB (PTB) and extrapulmonary TB cases (EPTB) respectively. The unit costs of a 6-month first-line treatment course, inclusive of monitoring tests, for an adult PTB case was US\$138 and US\$133 for a child PTB case. Drug-resistant TB (DR-TB) treatment was only observed in adults, and costed US\$2347 for an 8-month short regimen and US\$5940 for the 18-month long regimen. The unit costs per output highlighted variations between the BU and TD costing approaches such as a US\$10 variance for PCF, and a US\$20 variance for first-line treatment. Overall, the TD cost estimates were higher than BU estimates, as they capture more inefficiency (breaks, downtime and leave) than BU estimates.

**Conclusions:** This comprehensive unit costs database and the costing process has built capacity within the NTLD-P and international TB research networks, which will inform future TB budgeting processes in Kenya.

### EP16-255-22 The cost of reaching agricultural workers for TB prevention and treatment services in South Africa

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**Background and challenges to implementation:** While the prevalence of TB and access to prevention, treatment and care services has been studied elsewhere on the African continent, there has been little to no work published on the costs of providing tailored health services to potentially high-risk and vulnerable populations in South Africa. Given possible occupational exposures and long distances from health facilities, agricultural workers are at special risk for TB in South Africa and require tailored services for improved case finding and treatment adherence support while ensuring cost-efficiency in utilizing limited resources.

**Intervention or response:** As part of the USAID TB South Africa Project, we implemented a community and workplace-based outreach, screening and adherence support intervention in Western Cape and Eastern Cape provinces in South Africa beginning in April 2017. The intervention includes community and workplace-based awareness events, screening campaigns, linkage to diagnostic and treatment services, and daily adherence support.

**Results/Impact:** From April 2017 to December 2019, the project reached 42,023 workers, of whom 94% (n=39,356) were screened, identified 637 people with TB (7.2% case yield) and successfully initiated 602 (95%) people on treatment. The costs incurred over this period were about \$112,909 USD, or about \$188 USD per patient initiated on treatment.

**Conclusions:** Given our high case yield and low cost of treatment initiation, TB screening, treatment initiation and adherence support should be expanded among agricultural workers with the goal of finding missing TB cases and ending the TB epidemic in South Africa.

### EP16-256-22 Cost-effectiveness analysis of three tuberculosis (TB) case detection methods implemented in Southwest Nigeria State of Lagos, Oyo and Osun

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**Background:** World Health Organization 2019 Global report put Nigeria case detection rate below 30% with about 300,000 missing TB cases. The problems of dwindling donor fund and lesser Government commitment to National TB control programme makes the situation more precarious.

Hence, evidence aimed to guide stakeholders on the most cost-effective approach for TB detection in resource limited country like ours is highly desirable.

This study evaluated the cost-effectiveness of three different TB case detection methods in three Nigeria Southwest Nigeria of Lagos, Osun and Oyo.

**Design/Methods:** A cross-sectional study was carried out, designed to determine the benefits of three different case detection methods in addition to routine Passive Case Detection (PCD).

The methods are: House to House Campaign (HHC) in slum areas, Household Contact Tracing (HCT) of an index case and Private Facility Incentive (PFI).

Data were collected retrospectively from the 2018 National TB programme recording & reporting tools and financial records of the States TB Control Programme. Effectiveness was measured as number of new cases detected and cost-effectiveness expressed as cost per case detected. Additional costs and effects of each method were estimated by comparing each method against PCD and expressed as incremental cost-effectiveness ratio (ICER). All costs were converted to the U.S. dollar.

**Results:** The ICER for HCT was \$30 per additional case detected at all contact levels and it was the most cost-effective method. At ICER of \$70 per additional case detected, HHC method detected more cases at a lower cost than the PFI, which was not cost-effective at \$161 per additional case detected.

Detection method	Cost (N)	Case detected	Incremental cost (NGN)	Incremental case	ICER (NGN)	ICER (\$)
PCD	65,900.00	1475	0.00	0	0.00	0.00
HHC	130,800.00	4033	64,900,000.00	2558	25,371.00	70.00
HCT	72,464,000.00	2057	6,564,000.00	582	11,278.00	31.00
PFI	95,170,000.00	1975	29,270,000.00	500	58,540.00	161.00

**Conclusions:** Complementing household contact tracing with routine passive case detection is the most cost-effective approach to detect new TB cases. We recommend that it should be strictly followed and should be prioritized in our implementation plan for increased TB diagnosis in Nigeria.



### EP16-257-22 An evaluation of the feasibility and costs associated with a private-sector engagement pilot for pharmacies in Ho Chi Minh City, Viet Nam

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**Background:** Pharmacies represent the initial point of care seeking for an estimated 50-70% of people with TB. Friends for International Tuberculosis Relief has been implementing a private clinician engagement scheme in Ho Chi Minh City, Viet Nam since 2017, but had not yet systematically engaged private pharmacies.

**Design/Methods:** This pilot used the SwipeRx pharmacy professional social networking app to recruit pharmacists, facilitate verbal screening, and refer eligible people for CXR screening and diagnostic testing between 12-Oct and 31-Dec 2020. Pharmacists received incentives for screening, successful CXR referral and detection of TB. The pilot's yields were analyzed along the TB care cascade and the cost of incentives per TB detection were calculated and compared to costs from FIT's private clinician referrals.

**Results:** 146 pharmacists were recruited and trained. 182 pharmacy customers were referred for CXR, resulting in 64 (35.2%) CXRs being performed and the detection of 7 TB patients. The pilot achieved a Number Needed to Screen of just 26 (NNS) and to Test of just 9 (NNT). 54 pharmacists made at least one referral (36.9% of those trained) during the pilot period. However, just 2 pharmacists accounted for 31.3% of all referrals, while 35 pharmacists made just one or two referrals. The cost of incentives was lower for pharmacy referrals compared to clinician referrals (USD 64.07 vs USD 126.21 per TB detection) due to the higher TB yields among pharmacy referrals.

**Conclusions:** This pilot showed that it is feasible to engage private pharmacists for early TB detection and that costs are similar or lower compared to engagement of other types of private providers. However, large loss to follow up along the TB care case cascade was documented and yields were dependent on a small number of champion pharmacists. Further evaluations are needed to understand the scalability of this pilot.

### EP16-258-22 Cost-effectiveness analysis of 9-month MDR-TB treatment regimen, as evaluated within the STREAM trial. Further presentation of differences in food-supplement spending and working-hours disaggregated by sex

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**Background:** The STREAM Stage 1 trial demonstrated that the Short-regimen reduced health system costs by 20-25%, and was associated with an earlier return to work and a reduction in the purchase of supplementary food. The health economic data collected permit a number of secondary analyses, including differences patient costs by gender, and probabilistic estimates of the likelihood that the Short-regimen is cost-effective.

**Design/Methods:** Patient data were collected at 12-week intervals from the start of treatment up to week 132. Mean spending and mean working hours at each week were estimated by gender. Probabilistic sensitivity analyses were conducted via bootstrapping trial data for both Ethiopia and South Africa. The probability of cost-effectiveness was estimated for each country, at a range of willingness-to-pay thresholds for the trial primary outcome.

**Results:** Men spent \$221 (Short-regimen) or \$249 (Long-regimen) more than women on supplements. Although men reported working longer hours than women, the difference was not substantial. From a health system perspective, the probability that the Short-regimen is cost-effective is above 95% if the willingness to pay threshold for each additional favourable outcome is less than US\$19,000 in Ethiopia and US\$14,500 in South Africa.

**Conclusions:** Our results suggest that expenditure on supplementary food is a more important driver of gender differences in MDR-TB patient costs than hours worked, irrespective of regimen. They also suggest that the Short-regimen is highly likely to be cost-effective, although the trial primary outcome was a composite for which a willingness-to-pay threshold was challenging to determine precisely. Further research is required to determine why more was spent by men than women on supplementary food, and to establish relevant willingness-to-pay thresholds for MDR-TB favourable treatment outcomes.

**EP16-259-22 Cost analysis of the diagnostic cascade among patients with presumed pulmonary tuberculosis searching for care at a public health center in Rio de Janeiro, Brazil**

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**Background:** World Health Organization (WHO) currently considers the costs of patients and families as one of the barriers to fight tuberculosis (TB) and defines universal access to healthcare and the reduction of socioeconomic inequities associated with TB as a priority for the elimination of the disease. We aimed to analyze the direct and indirect costs incurred in the diagnosis of pulmonary TB among patients with presumed TB (PrTB) searching for care at a municipal health center in the metropolitan region of Rio de Janeiro.

**Design/Methods:** A cross-sectional, descriptive-analytical study was carried out from July 2017 to July 2019. We used the questionnaire endorsed by the WHO in the “Tuberculosis Patient Cost Surveys: a Handbook” 2017. Poverty line was defined as per capita income up to \$ 1.9/day, updated by the latest Purchasing Power Parity (World Bank).

**Results:** 256 patients with PrTB were eligible, 181 were recruited (71%) and among them, 120 (66%) patients were diagnosed with TB. Median time to diagnosis or exclusion of TB was 1.2 months (IQR 1.0 - 2.2) and the median number of visits to diagnosis was 3 visits (IRQ 3 – 4 visits). Total costs (median) incurred in the diagnostic cascade to confirm or exclude pulmonary TB were US\$ 476.00 (IQR 112.7 – 1473.05), mainly due to indirect costs (US\$ 272.54; IQR 15.0 – 1319.18). The economic impact of the diagnostic cascade was higher in TB patients, with an increase from 5% to 30% of patients below the poverty line vs. 13% to 18% in non-TB patients.

**Conclusions:** Although free access for TB diagnosis and treatment is offered in Brazil, time to diagnosis is long and the associated costs are high. There is an urgent need to adopt local public policies that increase access, helping the patient to reach the services faster and with lower costs.

**EP16-260-22 Setting chest X-ray abnormality thresholds to conduct validation of artificial intelligence vendors and ensure targeted and cost effective GeneXpert testing for abnormal X-ray persons**

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**Background and challenges to implementation:** Minimal expertise in measuring performance of AI software and low specificity of CXR reading may lead to excess number of GeneXpert tests of false positive “abnormal X-ray” cases corresponding to high GeneXpert testing costs and HCW staff time spent.

**Intervention or response:** Nearly 1,500 anonymized chest X-rays from the Lao PDR NTP dataset were analyzed by multiple AI vendors. A validation tool was developed on MS Excel to assist the Lao PDR NTP in selecting the most accurate AI software. Further, an abnormality threshold was set to ensure the software is able to refer abnormal X-ray cases for follow up GeneXpert testing in a targeted and cost effective manner.

Each X-ray analyzed by an AI provider came with a probability score, i.e. probability of having TB. Abnormality threshold is defined as the point above which a patient is considered to have an abnormal TB X-ray and is referred for follow up GeneXpert testing. We studied performance characteristics of the software across different thresholds and chose the probability at which the program found the maximum cases using minimum tests (costs).

**Results/Impact:** As can be seen in the attached image, at a \$15 testing (all-in) cost, at 50% threshold (default) the number of GeneXpert test is 334 (\$5,010) which is more than 2x if the threshold is 65% (165 tests at \$2,475). At both these thresholds all patients who were bacteriologically positive (retrospectively) would have been found. At 65% threshold we may have missed out on a few clinically diagnosed cases (98% accuracy) but the software would have found additional clinically diagnosed cases which human reading may have missed.

Abnormality Threshold	% of bacteriologically positive TB cases who would have detected as abnormal	% of all *bacteriologically positive and clinically diagnosed TB cases who would have been detected abnormal	Number of GX tests (# of abnormal)	Positivity rate on GeneXpert	GX Testing cost
45%	100%	100%	444	3.4%	\$ 6,660
50%	100%	100%	334	4.5%	\$ 5,010
53%	100%	100%	285	5.2%	\$ 4,250
55%	100%	100%	262	5.7%	\$ 3,930
60%	100%	100%	213	7.0%	\$ 3,195
64%	100%	100%	175	8.6%	\$ 2,625
65%	100%	98%	165	9.1%	\$ 2,475
70%	100%	98%	130	11.5%	\$ 1,950
75%	99%	90%	91	15.4%	\$ 1,365

[Table.]

**Conclusions:** A correct threshold (between 65 to 70% in our case) can ensure targeted GeneXpert testing so that minimum cases are missed while saving GeneXpert costs at scale by more than 50%.

## EP16-261-22 Charging user fees is not a predictor of number of TB cases detected among private health facilities in Nigeria

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**Background and challenges to implementation:** The US-AID-funded SHOPS Plus program supports screening and testing of presumptive TB clients in clinical facilities in Lagos and Kano States to increase access to care through the private sector. Clinical facilities (hospitals and nursing homes) are allowed to charge a fee within an agreed range (\$0-\$97) for registration, follow-up tests and six months of consultations. Private sector engagement is new and it was unclear whether fees affect case detection rates. We hypothesized that charging user fees is not associated with higher/lower TB case detection.

**Intervention or response:** Monthly TB program data from 2019 were reviewed. Linear regression was used to predict associations between charging user fees and the number of TB cases found after controlling for screening and testing rates.

### Results/Impact:

- 542 clinical facilities were reviewed; 423 (68%) in Lagos and 119 (22%) in Kano
- 440 (81.2%) were hospitals and 102 (18.8%) were nursing homes
- 374 (69%) charged fees while 168 (31%) offered free TB services
- 305 (69.3%) hospitals and 69 (67.6%) nursing homes charged fees
- The median screening rate of fee charging facilities was 34.4%, (CI 28.3%, 40.0%) which is lower than free facilities' screening rate of 51.7%, (CI 35.8%, 65.6%) ( $p < 0.001$ )
- There was no difference in the median testing rates between free (90.9%) and charging facilities (89.7%) ( $p = 0.923$ )
- The median number of TB cases found by fee charging facilities, 3 (CI 2, 3) was lower than free facilities 4 (CI 4, 5) ( $p = 0.117$ )
- Regression analysis estimated that charging user fees did not contribute to explaining the number of TB cases diagnosed in Lagos (Beta 0.009,  $p = 0.856$ ) and Kano (Beta 0.098,  $p = 0.258$ ) when controlling for screening rate and testing rates

**Conclusions:** The decision to charge fees for TB services among private sector providers does not negatively impact their performance in terms of TB detection.

## EP16-262-22 Cost effectiveness analysis of proposed TB diagnostic algorithm using the Loop-mediated Isothermal Amplification (TB-LAMP) among presumptive TB patients in the Philippines

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**Background:** A series of local evaluation studies were conducted to assess the effectiveness of the Loop-mediated isothermal amplification for TB (TB-LAMP) as a rapid molecular TB diagnostic tool. This paper will look into the cost-effectiveness analysis of employing TB-LAMP as a primary diagnostic tool in detecting pulmonary tuberculosis among for presumptive drug susceptible TB patients in the Philippines.

**Design/Methods:** A decision tree analysis model was designed to evaluate the cost effectiveness of the interventions and simulate outcomes of TB-LAMP, DSSM and Xpert as diagnostic assessment strategies for a hypothetical cohort of 10,000 presumptive adult PTB patients. Outcome measures were direct medical costs, opportunity costs, quality-adjusted life years (QALY) and incremental cost effectiveness ratio (ICER). The cost estimates and probability was undertaken using the data from local evaluation studies existing published literature and experts opinion.

**Results:** Program and operation cost is lowest with DSSM by > 50% compared with other strategies but unlikely to achieve maximum diagnostic potential given its low sensitivity and specificity and lowest QALY gained. Xpert yields high sensitivity, high QALY but higher program cost specially for remote testing areas. Sensitivity analysis reports that using PURE-TB-LAMP is a most cost-effective option for point of care facilities with high testing workload and are resource limited given the ICER of approximately USD80 and lower mortality rate.

Cost-effectiveness of the diagnostic tool and algorithms are affected by the number of patients screened, quality of life of patients if left undiagnosed and treated, and the efficiency of existing diagnostic algorithms.

**Conclusions:** Rapid and cost-effective strategies should be considered for use in national programs for TB control. Further comparative economic evaluation of using TB-LAMP is needed to determine its economic relevance to public healthcare to support policies in scaling up program as this may vary depending on program conditions.

## EP17 Facing TB during the COVID-19 pandemic

### EP17-263-22 Overcoming challenges of sample transportation for TB testing during COVID-19 lock down from 23rd March -30th April 2020 - an interventional study in Telangana, India

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**Background and challenges to implementation:** Early diagnosis and initiation of TB treatment is the key to successful treatment outcome under National TB Program in India. During the lockdown period due to COVID -19 from March 22nd 2020 to April 30th 2020 the diagnostic services of TB faced decline in numbers due to reduced number of samples reaching the diagnostic centers. This effected the early diagnosis of both TB and Drug Resistance TB hampering the program policy of universal drug susceptibility testing of all the diagnosed TB samples.

Due to the lock down there was a complete shutdown of outpatient services in the state. This led to reduced number of patients attending the OPD resulting in less number of sample collection. The health staffs on emergency duty further struggled in transporting the samples to the designated testing labs due to unavailability of courier and transport services.

**Intervention or response:** As per Government directives to not to discontinue TB services, State TB Office, Telangana took an initiative of delivering the TB drugs to the districts by 104 ambulance. All District TB Officers were instructed to send the samples collected from the field packed in a three-layer package boxes as per the guidelines in the same ambulance when they reach to deliver the TB medicine.

**Results/Impact:** A total of 291 samples were received for Gene Xpert testing and 2151 samples were received for Line Probe assay and 394 samples for liquid Culture and drug susceptibility testing.

**Conclusions:** This intervention helped in providing uninterrupted diagnosis and treatment to all the TB patients even during the lockdown period.

## EP17-264-22 Tuberculosis patients through tele communication in COVID situation: BRAC experience

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**Background and challenges to implementation:** World is fighting to end infectious diseases such as TB, malaria, and HIV for a better and communicable disease-free world. Unprecedented new infectious diseases are emerging. The world is crippling towards the grip of a recent pandemic of SARS-CoV-2 named as COVID-19. Unfortunately, Bangladesh has detected more than 16,000 COVID cases so far after the detection of the first COVID-19 cases on the 8th March 2020.

**Intervention or response:** Field monitoring and supervision, strengthened contact tracing through a mobile phone or virtual meeting platform have been ensured. A separate reporting format has been introduced to the field in relation to telecommunication, follow up status, stock status etc. All TB staff were trained on COVID-19 awareness, and infection control using guidelines and online training by March 2020.

**Results/Impact:** In March-April, 2020, A total of 2496 (97%) TB staff out of 2570 were received training. Currently, ongoing TB patients were 98,460. Among these, 83367 (84%) TB patients were monitored by Tele Communication, where 97617 (98%) have received DOTs on a regular basis and 81703 (83%) had anti TB drugs in hand for at least 7 days. less than 718(1%) patients did not (2nd, 5th month and end of the treatment) receive follow-up sputum tests within a stipulated time.

**Conclusions:** Planned, repurposing and effective utilization of resources can ensure uninterrupted TB service during a pandemic situation. However, to increase TB presumptive and case finding in a lockdown situation are very challenging.

## EP17-265-22 Physically distant but still in contact: telephonic counseling for rifampicin-resistant tuberculosis patients in South Africa during the COVID-19 pandemic

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**Background and challenges to implementation:** Corona virus disease 2019 (COVID-19) threatens to undermine progress in the global tuberculosis (TB) response by disrupting routine TB services. People living with TB, including rifampicin-resistant (RR) forms, are likely at additional risk of severe COVID-19. Innovative strategies are needed to ensure RR-TB services are modified to minimize routine clinic visits to reduce COVID exposure, while still maintaining patient support. We describe implementation of a mobile health (mHealth) intervention to provide telephonic counseling offered to RR-TB patients in Khayelitsha, South Africa during the COVID-19 pandemic.

**Intervention or response:** As standard of care, all patients initiated on RR-TB treatment in South Africa receive facility-based counseling by lay RR-TB counselors. In order to minimize RR-TB patients' facility-contact, telephonic counseling sessions were provided to all RR-TB patients newly initiated on treatment from March 1, 2020 (Table 1).

**Results/Impact:** Some early benefits include: the ability to follow patients including those who require daily adherence support; a decrease in facility visits to minimize COVID risks and reduce patient costs. Challenges include: a lack of buy-in from staff at RR-TB facilities and thus not all patients are referred for telephonic RR-TB counseling; the lack of reliable phone access (including charging facilities) in patients' homes; patients not answering calls coming from a landline; and challenges in developing rapport and trust over the phone. This approach is continually reviewed to ensure that the needs of patients are addressed during this pandemic.

**Conclusions:** Innovative models of care are needed to ensure RR-TB patients receive appropriate and enhanced support despite the need for decreased interactions with facilities during the COVID-19 pandemic. mHealth interventions should be explored for routine practice even beyond COVID-19 as they might alleviate some of the burden frequent visits place on patients.

Standard Counseling	Modifications to counseling in view of COVID-19
Two in-person counseling sessions on RR-TB treatment literacy	Done telephonically
Substance-use screening and a brief substance use counseling intervention if needed	Done telephonically
Home visit to assess and provide information about infection control and counsel family on RR-TB	A home visit was substituted with a telephonic session unless deemed an emergency to conduct a home visit for specific patients Where patients have given disclosure permission: family counseled over the phone on RR-TB  Additions: <ul style="list-style-type: none"> <li>Information on COVID-19 infection control measures shared during counseling for those with concerns</li> <li>Counselors liaise with facilities to confirm routine follow up dates and times to minimize patient wait times</li> </ul>

[Table 1. Modifications to the counseling offered to RR-TB patients during COVID-19]

## EP17-266-22 Programmatic adaptations to the treatment of rifampicin-resistant tuberculosis infection in children and adolescents during COVID-19

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**Background and challenges to implementation:** The corona virus 2019 (COVID-19) pandemic challenges the effective post exposure management of persons exposed to rifampicin-resistant tuberculosis (RR-TB). South African guidelines recommend treatment for high-risk RR-TB contacts where active TB disease is ruled out. The pandemic has made clinics potential hotspots for COVID-19 and has disrupted TB services, putting RR-TB contacts at higher risk of developing RR-TB (in turn increasing risk of COVID-19 complications).

**Intervention or response:** Médecins Sans Frontières has supported the department of health's implementation of post exposure management guidelines for children and

adolescents exposed to RR-TB in Khayelitsha, South Africa since 2017. Post exposure management services were modified in view of COVID-19 as demonstrated in Table 1.

Standard post exposure management	Modified post exposure management during COVID-19
-Asymptomatic contacts are recalled to the clinic for clinical consultation in order to determine if TB disease is present or to determine eligibility for treatment of infection if no disease is present and the contact is deemed high first	-Contacts that were present during home visits conducted for RR-TB patients, and those that accompanied an index case to the clinic were assessed for symptoms and, where relevant, were started on treatment of infection - Asymptomatic contacts were only recalled to the clinic if they were identified remotely as having TB symptoms, or if they were considered very high risk of TB disease (eg. Under 5 year olds)
-Initiation of treatment of infection at the facility for those eligible	-Contacts identified as particularly high risk and vulnerable to developing RR-TB (e.g. under 5 years) were screened and initiated on treatment for infection during a home visit -If this was not possible contacts were called to a facility and clinically reviewed with rigorous infection control practices -For those started on treatment, multi-month medication refills were provided (delivered to the home or given to the index case)
-Two monthly clinical follow-up to access clinical condition and to assess and treatment modifications needed	-Follow-up visits were conducted telephonically through a mobile health (mHealth) intervention

[Table 1. Modifications made to post exposure management during COVID-19]

**Results/Impact:** Fourteen children and adolescents have received treatment of infection from March-April 2020 during the COVID-19 pandemic. Successes have included: fewer visits to the clinic thus saving time and money for contacts and allowing for more frequent follow-up sessions; more time for the contacts to ask health related questions without being time pressured, thus fostering better relationships with their clinician; less health resources consumed. Conversely, challenges have included trouble reaching patients with no cell phones or incorrect numbers. In such cases the health care workers have investigated alternative methods of contacting the patients, including conducting home visits. Home visits were also challenging in cases in which the contacts were living in areas with safety concerns.

**Conclusions:** It is imperative that communities affected by RR-TB, particularly children and adolescents who are already a vulnerable group, are not forgotten during the COVID-19 pandemic. Innovative interventions – including mHealth, and community models – should continue to be explored to provide services to these patients while minimizing risk of COVID-19 infection.

## EP17-267-22 Collaboration in tuberculosis and COVID-19 control in Bungoma County

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**Background:** World Health Organization (WHO) declared novel COVID-19 as a global pandemic on 11 March 2020. COVID-19 has several health systems challenges which directly or indirectly affect tuberculosis (TB) services. Preliminary data shows tuberculosis (TB) diagnosis has been impacted negatively by the pandemic. This is due to the overlap of TB and COVID-19 symptoms, restrictions placed on movement affecting case finding, and stigma attached to the symptoms. COVID-19 and pulmonary TB both affect the respiratory system and people with COVID -19 may show similar symptoms to TB such as cough, fever and difficulty in breathing. It's a policy that patients seeking health care in all health facilities are screened for COVID-19. We aimed to screen all patients seeking health care in Bungoma County, for COVID-19 and TB concurrently during world TB commemoration week.

**Design/Methods:** All patients were screened for COVID-19 by use of COVID-19 screening tool; those who screened positive, samples were taken for COVID-19 test. All patients were also screened for TB using TB structured questionnaire. Those who had presumptive TB were evaluated for TB.

**Results:** A total of 3262 patients were screened for both COVID-19 and TB, 234 (7.1%) had presumptive TB, 224(95.7) were evaluated for TB and 12(5.4%) were TB positive and they were all linked to care. A total of 31 (0.9%) met the case definition of COVID-19, samples were taken for testing and they were all negative.

**Conclusions:** Complementally COVID-19 and TB response is critical during this pandemic. Both diseases can utilize the capacity building efforts, surveillance and monitoring system put in place. Patients with mild/moderate symptoms of COVID-19 are currently being asked to self-isolate at home. However, these symptoms overlap with those of TB and it is important that such patients are investigated for TB appropriately.

## EP17-268-22 Connecting the DOTS during the COVID-19 pandemic: using community structures and the private sector to establish linkages for increased TB case detection in Nigeria

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**Background and challenges to implementation:** COVID-19 restrictions and social distancing threaten to halt USAID's SHOPS Plus social and behavior change (SBC) activities in Nigeria, limiting case finding and increasing potential for TB community spread. Symptom similarity between COVID-19 and TB may also worsen stigma and misconceptions further threatening TB case identification. SHOPS Plus used a tailored SBC strategy during the COVID-19 pandemic to ensure continued community focus on and involvement in TB case detection.

**Intervention or response:** SHOPS Plus's SBC strategy is rooted in education and mobilization through the engagement of providers and community leaders (religious and business) – but this had to be rapidly strengthened and community-led when COVID-19 lock-downs began. With lock-downs imminent the program identified local medicine vendors to sensitize existing community structures about TB and conduct small-scale outreach events for screening and testing. SHOPS Plus mapped out communities surrounding its provider networks' clinical hubs to identify medicine vendors to integrate TB education into their provider associations' routine meetings and recruit sensitized community volunteers as cough monitors. SHOPS Plus trained cough monitors on TB symptoms to aid identification of presumptive TB cases and refer them to the medicine vendors or clinic hubs. SHOPS Plus also continues to provide virtual support along with educational flip-charts and brochures for distribution through community structures increasing TB awareness and providing directions for accessing TB testing and treatment.

**Results/Impact:** By working with local providers and community leaders to maintain TB education, screening, referrals and linkage to treatment, SHOPS Plus mitigated a potential halt in TB case detection in the private sector in Lagos and Kano States in the midst of the COVID-19 pandemic.

**Conclusions:** Within the limits of COVID-19 infection control protocol, TB detection in Nigeria can benefit from innovative strategies which require minimal travel and costs, using existing community structures to increase education and participation in TB case finding.

## EP18 Scaling up TB preventive therapy: it is about time!

### EP18-269-22 TB contact investigation in 17 municipalities of Uganda - bringing TB screening to the household – way of coalition with communities

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**Background and challenges to implementation:** About half of TB patients in Uganda are missed by the health-care system each year<sup>1</sup>. This causes continuous transmission in a population with 253/100,000 TB and 7% HIV prevalence respectively and 50% under 14 years. Each patient could infect 10 people per year. Unfortunately, Uganda's approach to finding TB has traditionally been passive. This jeopardizes the response to the TB fight. We carried out joint (by community-based and health facility-based health workers, HWs) TB contact investigation (CI) to ensure early, provider-initiated, community-engaging TB diagnosis.

**Intervention or response:** Over seven quarters, Uganda Stop TB Partnership plus districts engaged community actors in designing, planning and implementing this intervention. Training on TB CI for both categories of HWs and provision of tools, sputum packaging materials were done. HWs collected data on index patients and their contacts; visited the contacts, carried out health education on TB and CI. They screened contacts, collected sputum from those with suspected TB, referred legible ones for further evaluation. At facilities further evaluation, testing for TB and drug resistance was done. Patients were started on treatment.

**Results/Impact:** 2780 index patients were recruited, 16,965 contacts screened, 4,014 people with suspected TB investigated, 481 patients diagnosed – a yield of 12% among people with suspected TB. Of the 481 patients, 475 were started on treatment. The approach could have enhanced community-supported, patient-centered TB care, ensured early diagnosis, interrupted transmission.

Quarter	Total attendance	Screened	% screened	For TB evaluation	% for evaluation among screened	TB patients
Q1 2018	132,938	3,297	2.5	5	0.15	1
Q2 2018	123,972	2,442	2.0	10	0.41	0
Q3 2018	137,520	63,025	38.6	8	0.02	2
Q4 2018	125,775	65,403	52.0	450	0.69	34
Q1 2019	141,128	69,152	49.0	920	1.33	64
Q2 2019	110,300	71,695	65.0	913	1.27	72
Q3 2019	130,750	104,600	80.0	1,059	1.01	83
Total	902,383	369,614	41.0	3,365	0.91	256

[Table. Results of engaging PHPs in TB care and prevention services]



**Conclusions:** The results demonstrate the importance of engaging the community in planning and implementing systematic CI as a TB finding method. Letting community players lead household activities is recommended. The approach can be used to integrate TB preventive therapy and HIV services into TB services; can also be used in other community-based health interventions focusing on early diagnosis in areas where communities have barriers in accessing services at facilities. It can lay ground for strengthening community systems.

### EP18-270-22 Breakthrough TB among people living with HIV on isoniazid preventive therapy in Zambia

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**Background:** Isoniazid preventive therapy (IPT) has been proven effective for the prevention of TB in people living with HIV who are at high risk for progressing to active TB after being latently infected with TB. However, it has been observed that some patients develop active TB disease while taking TB preventive therapy. This is referred as breakthrough TB. This study aimed to determine the incidence and profile of patients with breakthrough TB.

**Design/Methods:** A retrospective analysis of IPT programme data collected between October 2016 to October 2019 from CDC/PEPFAR supported primary health facilities under the ACHIEVE project in Lusaka, Western, Eastern and Southern provinces in Zambia was done.

**Results:** A total of 48581 PLHIV were enrolled on IPT from October 2016 to October 2019. Of these, 130 (0.3%) developed breakthrough TB. Out of the 130, only 90 client records were accessed. The median age for the study sample was 35 with more males than females 58:32. Of these, 24% were symptomatic at the beginning of IPT, 20% were asymptomatic and others had missing data. Seventy five of the 90 (83%) breakthrough TB cases developed TB in the first month, 10% in month 2, 4% month 3 and 1% in month 4-6 of IPT. Rifampicin resistance was detected in 1 patient, no patient had data on isoniazid resistance.

**Conclusions:** Breakthrough TB does occur while patients are taking TB preventive therapy. Most cases occurred during the first month of IPT initiation suggesting missed diagnosis of TB during the screening process for IPT and possibly immune reconstitution inflammatory syndrome. Effective TB screening before administering IPT is essential to avoid inadvertent isoniazid monotherapy for active TB and to reduce the incidences of breakthrough TB. Surveillance for isoniazid resistance in patients who develop breakthrough TB needs to be done.

### EP18-271-22 Tuberculosis preventive treatment: global targets and progress to date

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**Background and challenges to implementation:** About one quarter of the world's population is infected with tuberculosis (TB) bacilli and 5-10% of them will develop active TB in their lifetime. Tuberculosis preventive treatment (TPT) is a key scalable intervention, without which the levels of reduction in global TB incidence envisaged by the End TB Strategy will not be achieved. Member States at the United Nations High-Level Meeting on TB in 2018 (UNHLM) committed to treat by 2022 at least 6 million people living with HIV (PLHIV), 4 million contacts of TB patients aged <5 years and 20 million contacts aged >5 years. Achieving this will require coordinated activities to identify and treat eligible populations safely.

**Intervention or response:** We present recent trends in TPT coverage using data from annual country TB reporting to the World Health Organization (WHO).

**Results/Impact:** Based on reporting by 65 countries, 1.8 million PLHIV started TPT in 2018, up from <1 million in 2017 and a massive increase from <30,000 people newly enrolled in HIV care in 2005. About 1.3 million children aged <5 years were estimated to be contacts of bacteriologically-confirmed pulmonary TB patients in 2018. In 2018, 109 countries reported 349 487 contacts aged <5 years starting TPT, an increase of 20% from 2017. Sixty-nine countries reported 79 195 contacts aged >5 years starting TPT, a decrease of 30% from 2017.

**Conclusions:** While the UNHLM target for TPT coverage in PLHIV looks to be achievable, it is unlikely that countries will start 24 million contacts on TPT, particularly those aged >5 years. Nonetheless, political commitment, stronger advocacy by technical and funding agencies matched with more resources, the new WHO guidance on TPT, the recent reduction in the price of rifampentine-containing regimens and the advent of new regimens and drug formulations are recent developments that hold promise for overcoming key barriers to expand TPT coverage.

### EP18-272-22 Understanding barriers to latent tuberculosis treatment in people living with HIV in Cambodia: results from the KAP survey and facility assessment from the OPTICAM study

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**Background:** Despite national recommendations for tuberculosis (TB) preventive therapy (TPT) for people living with HIV (PLHIV) in Cambodia, the coverage is estimated <30%. Phase 1 of the OPTICAM study aims to identify barriers to prescribing and initiating TPT.

**Design/Methods:** A Knowledge, Attitudes, and Practices (KAP) survey was self-administered to two clinicians and two nurses/midwives in October-November 2019 from 28 HIV-care sites in five provinces of Cambodia to assess health care workers' (HCWs) barriers to TPT. A Facility Assessment was conducted to understand functional barriers. Data were entered into REDCap database and analyzed using MSEXCEL16 and SAS9.4.

**Results:** The KAP showed that 91% of HCWs believe TPT is important for PLHIV. 82% felt confident in ability to rule out active TB. However, the facility assessment showed challenges in TB diagnosis such as patient ability to produce sputum (46% of facilities) and difficulties to interpret chest x-ray (43% of facilities). The main challenge for using GeneXpert is non-functional modules (38% of facilities).

30% of HCWs have received LTBI training, but 74% report that lack of adequate training keeps them from initiating TPT, and 87% think further training would be beneficial. 35% of HCWs have faced Isoniazid stock shortages and 88% were concerned about risk of drug stock-outs when initiating TPT. Concerns of drug resistance (20% of respondents) were mentioned by HCWs, as well as concerns of side-effects (20% of respondents); this was also the main reason for patient refusal of TPT, which occurred at 25% of facilities. In the KAP, 49% believed using TPT concomitantly with ART compromised ART efficacy.

**Conclusions:** Targeted trainings on TPT, focusing on eligibility criteria, side effects and drug-drug interactions, should be conducted to improve initiation rates. Strengthening the TPT drug supply is necessary for increased confidence in initiating TPT; using a shorter TPT regimen can help to ease drug supply concerns.

### EP18-273-22 Tuberculosis preventive therapy amongst contacts above 5 years in line with United Nations High-level Mission commitment; the journey so far in Nigeria

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**Background and challenges to implementation:** About 490,000 Nigerians are estimated to have Tuberculosis diseases, among this number of cases 75% are undetected yearly. The challenge in the system is not just the undetected cases but the majority of contacts of index cases who may show no signs or symptoms of TB disease and are at risk for developing active TB disease if not identified early for preventive therapy. Several studies have shown that, on average, 5–10% of those infected with *M. tuberculosis* will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection leading to increase in disease incidence. During the 2018 UNHLM, the scope of LTBI management was broadened to include contacts above 5 years (including adults). Nigeria adopted this global policy and started implementation from January 2019.

**Intervention or response:** Routine data collected by the National TB programme between January to December 2019

**Results/Impact:** A gradual uptake of TPT among >5 years contacts was noticed from January 2019. The total number of contacts placed on TPT was 394 (82% of total contacts eligible) in Q1, 116 (57% of eligible) in Q2, 156 (75% of eligible) in Q3, to 350 (36% of eligible) in Q4. Annual >5 placed on TPT is 1,016 out of 1860 eligible which is 55% placement. When compared to <5 which is the traditional cohort placed on TPT a huge difference is seen with about 92% of eligible placed on TPT. 2488 (88% of eligible) in Q1, 2358 (92% of eligible) in Q2, 2639 (93% of eligible) in Q3, 2287 (95% of eligible) in Q4.

**Conclusions:** Approach to ensure increased identification of eligible >5years for placement on TPT is essential as that population covers a wide range of age and should have more population. Shorter TPT regimen is key in ensuring TPT completion rate.

### EP18-274-22 Prevalence of latent tuberculosis (TB) infection among household contacts of TB patients in a low-resource, high-TB/HIV burden setting

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**Background:** The WHO recommended the scale up of programmatic management of latent TB infection (LTBI) as a key component of the End TB Strategy. The scale-up includes testing for LTBI to identify persons at increased risk for developing TB who would benefit most from TB preventive therapy (TPT). However, the proportion of interferon gamma release assay (IGRA) positive household contacts (HHCs) in Uganda that would require TPT was unknown. We sought to determine the prevalence of IGRA positivity among HHCs.

**Design/Methods:** From February 17 to March 6, 2020, we conducted a cross-sectional survey at four tertiary referral hospitals. HHCs of AFB/GeneXpert positive TB patients who did not show signs and symptoms of TB were included in the study. The study team excluded HHCs who were <5 years, in contact with drug resistant TB patients, and/or had a history of TPT or TB treatment. Using the open data kit mobile application, we collected data on participant characteristics and tested HHCs for both HIV (using Determine® & Stat Pack®) and LTBI (using Quantiferon-TB-Gold-Plus®). We performed multivariate logistic regression using STATA version 14 to determine the associations between IGRA positivity and participant characteristics.

Test done	Positive	Negative	Indeterminate
IGRA test result	115 (32.7%)	231 (65.6%)	6 (1.7%)
	Positive	Negative	Declined
HIV test result	11 (3%)	314 (89%)	27 (8%)
Associations	Odds	P-value	95% Confidence Interval
Age of household contact >24 years	3.68	0.01	(01.37-10.38)
Contact was index patient's spouse	5.96	0.04	(01.08-04.40)

[Table.]

**Results:** Of the 355 HHCs identified, 352 (99%) consented to participate, 54% were female and 3% were HIV positive. The mean age was 24 years. A total of 115 (32.7%) had a positive IGRA test result. Positivity was

higher in persons above 24 years [OR 3.68 (95% CI 1.37-9.9)] and in spouses of index TB patients [OR 5.96 (95% CI 1.08-4.40)].

**Conclusions:** Given that LTBI was prevalent in one third of HHCs, wider use of IGRA testing has the potential to improve resource utilization for TB prevention by focusing TPT use on those who would benefit most from the intervention. We recommend IGRA testing among >5-year-old HHCs in similar high-burden resource-limited settings.

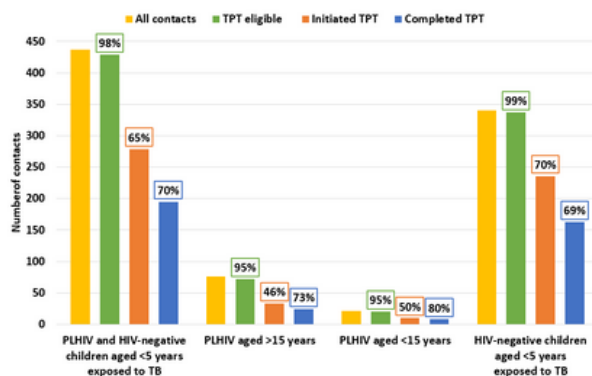
### EP18-275-22 Tuberculosis preventive treatment cascade among household contacts of persons with tuberculosis in Western Uganda (October 2017 - September 2018)

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**Background:** Household tuberculosis (TB) contacts are at high risk of TB infection. People living with HIV (PLHIV) and children aged <5 years are at high risk for progression to active TB disease and are prioritized for TB preventive treatment (TPT). We examined the TPT cascade among household contacts following active TB contact tracing including HIV home-based testing (HBT).

**Design/Methods:** We enrolled household contacts of all persons with TB from October 1, 2017 to September 30, 2018 in one district in Western Uganda. HIV status was determined by self-report and HBT. Contacts were screened for TB using a four-symptom screen per Ugandan guidelines. PLHIV and children aged <5 years with negative TB screen results or positive TB screen results with TB subsequently ruled out were TPT-eligible and referred for TPT initiation at nearby antiretroviral therapy (ART) clinic or TB clinic, respectively.

**Results:** Of 1692 contacts, 437 (26%) were PLHIV or aged <5 years: 76 (4%) PLHIV aged ≥15 years, 21 (1%) PLHIV aged <15 years, and 340 (20%) HIV-negative children aged <5 years. Of these 437 contacts, 429 (98%) were TPT-eligible: 375 (87%) had negative TB screen results, 38 (9%) had positive TB screen results with TB subsequently ruled out, and 16 (4%) had unknown results. TPT initiation among eligible contacts was 65% overall and was higher among HIV-negative children aged <5 years (236/337 [70%]) compared to PLHIV aged ≥15 years (33/72 [46%]) and PLHIV aged <15 years (10/20 [50%]) (Figure). TPT completion was 70% (195/279) overall.



[Figure. Tuberculosis preventive treatment cascade among household TB contacts, by HIV status and age in Western Uganda (October 2017 - September 2018)]

**Conclusions:** TB contact tracing including HIV HBT successfully identified TPT-eligible contacts. Lower TPT initiation among PLHIV relative to HIV-negative children aged <5 years may reflect differences in perceived TB risk or in capacity to implement (or document) TPT between ART clinics and TB clinics. Close monitoring and support for TPT completion could help improve outcomes for both subpopulations.

### EP18-276-22 Good proportion of household contact children age below 5yrs were TB screened but not getting preventive therapy in SNNPR and Addis Ababa, Ethiopia

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**Background and challenges to implementation:** Ethiopia made significant strides to improve management of latent tuberculosis infection (LTBI). Ethiopian national guidelines recommended a 6-month course of isoniazid (H) preventive treatment (IPT) for treatment of under-five children with LTBI until January 2019 when the country endorsed the recent WHO recommendations. Accordingly, HIV negative children <15 years of age who fulfill eligibility criteria will receive a three-month course of daily INH and rifampin (R). For people living with HIV, irrespective of age, the 6-month INH remains the standard treatment. The use of a three-month course of INH and rifampin (3HP) is endorsed as part of the nationally recommended regimens. In preparation to support the roll out new recommendations, we reviewed the rate of IPT initiation for eligible under-five children in two regions of Ethiopia.

**Intervention or response:** This study was conducted in the Southern and Addis Ababa regions of Ethiopia. We collected and analyzed secondary data for the period

Oct 2016 – Sept 2017. We extracted data from the standard of Care led mentorship database which captured important variables related to contact screening and provision of preventive therapy.

**Results/Impact:** Our baseline assessment showed that from 25% to 37% of bacteriologically confirmed index pulmonary TB patients were living with children of age < 5 years. Ninety-five percent of <5 year household contacts were screened for TB. However, the yield (diagnosis of TB in young children) of a one-time contact TB screening was < 0.15%. Of those screened, 92% were eligible for TB Preventive therapy but only 56% were put on preventive therapy.

Variables	SNNPR		Addis Ababa		Total	
	Number (n)	%	Number (n)	%	Number (n)	%
# of HH contact registered	12,727	100%	2,765	100%	15,492	100%
# of HH contact screened - all ages	12,102	95%	2,614	95%	14,716	95%
# of HH contact children age ≤ 5yr	1,417	11.7%	233	8.9%	1,650	11.2%
# of children contacts ≤ 5yr screened for TB	1,314	93%	220	94%	1,534	93%
# of ≤ 5yr contact eligible for IPT	1,305	92%	216	93%	1,521	92%
# of eligible children ≤ 5yr put on IPT	731	56%	116	53%	847	56%

[Table.]

**Conclusions:** Despite high rates of household contact screening, the rate of TPT initiation was low and information on TPT completion rate is lacking. Further interventions are needed to improve the TPT initiation rate and documentation of TPT completion rates.

### EP18-277-22 Implementation and scale-up of tuberculosis preventive treatment among people living with HIV - South Sudan, 2018 - 2020

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**Background and challenges to implementation:** Tuberculosis (TB) preventive treatment (TPT) decreases TB incidence among people living with HIV (PLHIV). In South Sudan, of the estimated 190,000 PLHIV in 2018,

31,000 were receiving antiretroviral treatment (ART). There were 1,900 PLHIV diagnosed with TB disease in 2018. Although 2017 national HIV and TB guidelines included TPT as standard HIV care, its use in clinical practice was limited, with supply and logistical barriers for its delivery to ART facilities.

**Intervention or response:** To facilitate TPT implementation and scale-up among PLHIV during 2018–2020, US President's Emergency Plan for AIDS Relief (PEPFAR) South Sudan and Ministry of Health (MoH) effected an intervention of three components: disseminating job aids for program managers and clinicians to enhance TPT delivery, conducting a TPT pilot program among PLHIV, and identifying a mechanism for procuring isoniazid for TPT.

Job aids included decision algorithms for TPT delivery among PLHIV, and trainings were conducted by PEPFAR-funded implementing partners (IPs) and MoH TB/HIV field supervisor staff in 2018. An MoH circular disseminated in June 2018 improved algorithm implementation. In 2018, during the TPT pilot program at Juba Teaching Hospital HIV Clinic, 54 eligible PLHIV initiated TPT, and 48 (89%) completed TPT.

**Results/Impact:** After introduction of the three components, TPT was implemented in 13 ART sites. During July–September 2019, 2,801 PLHIV initiated a six-month course of TPT. During October 2019–January 2020, TPT expanded to 24 sites, with an additional 1,125 PLHIV initiating TPT. In 2019, PEPFAR South Sudan delivered isoniazid for complete TPT courses for 12,700 eligible PLHIV. The intervention facilitated nationwide TPT use in a resource-limited setting.

**Conclusions:** TPT scale-up in resource-limited settings may require supplementing national guidelines with clinician guidance, training, and an implementation pilot. Collaboration of IPs and field supervisors can rapidly disseminate standardized TPT implementation and monitoring. Consistent commodities procurement ensures sustained TPT scale-up.

## EP19 Quality and modelling of TB

### EP19-278-22 Mathematical modelling of new TB diagnostics at subnational sites: evaluating the effects on health systems and patients across sites in same province with differing characteristics

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**Background:** There are multiple ways to diagnose tuberculosis, with competing methods providing different accuracies in their results, and varying in their length of time, and the demand they place on resources and patients. Understanding which strategy should be used in which circumstance is critical to policy makers when allocating health budgets.

**Design/Methods:** A detailed operational model was developed enabling comparison of impacts and cost-effectiveness of multiple diagnostic strategies for TB diagnosis in Cavite Province, Philippines. Detailed diagnostic data were collected from six drug-susceptible diagnostic facilities and two MDR-TB facilities in Cavite, chosen for their differences in geographical and epidemiological characteristics. Patients were interviewed about the costs they incurred along their diagnostic pathway, with these values used as model inputs. The Base-case and four further core strategies involving GeneXpert Ultra were evaluated. These considered Ultra alone and in combination with Chest-X-ray and microscopy.

**Results:** The optimum strategy for diagnostic yield was full rollout of GeneXpert Ultra for most sites, with the primary benefit coming from the additional identification of patients with MDR-TB, with this increase ranging considerably from 22% to 220% between sites. The benefits of rolling out Ultra varied substantially across the six sites across key outcomes including yield, drop in over-diagnosis and reduction in patient costs. The key influencing factors were today's level of clinical diagnosis, TB prevalence, patient-cost makeup and loss-to-follow-up rate. When considering a societal perspective, reduction in patient costs through reduced over-diagnosis could be influential in decision making.

**Conclusions:** The benefits found in newer diagnostics vary considerably at sites even within the same province, and policymakers should be wary of taking a one-size-fits-all approach. Though Ultra provided great benefits in MDR-TB detection, sites with high clinical diagnosis

in the Base-case saw little additional benefit in correct DS-TB identification with introduction of GeneXpert Ultra, as most true cases currently treated empirically.

### EP19-279-22 Social media as a tool to build capacity and efficient clinical decision-making for doctors working in resource limited setting

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**Background and challenges to implementation:** TB in Myanmar is more prevalent in hard-to-reach areas where drug use is endemic, healthcare system is fragile and civil conflicts are rife. Healthcare workers working in those areas are especially challenged in building their capacity and pursuing continuous medical education.

**Intervention or response:** The Asian Harm Reduction Network (AHRN) has been implementing harm reduction interventions integrated with TB prevention and treatment services in Northern Myanmar since 2007. Mobile TB active case finding teams equipped with portable digital X ray and laboratory facilities travel to remote rural hard-to-reach villages in Kachin, Shan State and Sagaing Region.

Medical doctors from AHRN received training on chest X-ray (CXR) interpretation and clinical management of TB from both National TB Program and in-house trainings. AHRN did set up a closed Facebook group where field doctors upload CXRs with clinical presentation through standard case discussion and receive technical support from an expert pulmonologist. All other medical colleagues learn from such case discussions. All doctors are assigned to upload one special case weekly and discuss among colleagues.

**Results/Impact:** Recent survey found that through this approach and ongoing case discussions in the group, the medical doctors are more confident on their clinical decision and have improved their skills in CXR reading and management of patients with presumptive TB. The presumptive TB screenings increased from 25,082 in 2018 to 28,399 in 2019. Number of all form TB cases increased from 1,062 (Bacterial confirmed 394) to 1,258 (Bacterial confirmed 423).

**Conclusions:** The clinical care of presumptive TB patients in remote areas can improve significantly by providing distance learning and effectively use of social media as a tool to improve knowledge and capacity. This should be practiced in other hard-to-reach areas to provide quality care and accessible health services. Efficient clinical decisions save many lives.

### EP19-280-22 Access to quality TB diagnostic services in Nigeria: the role of specimen transport systems

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**Background and challenges to implementation:** Since 2016, the National TB and Leprosy Control Program (NTBLCP) adopted and implemented the policy of using the GeneXpert machine as the primary TB diagnostic tool. With less than 45% geographical coverage (407 machines distributed across 774 LGAs) in 2019, USAID funded Challenge TB project (CTB) established and implemented a specimen transportation system using “hub and spoke” model. The hub is a tertiary or secondary health facility with a GeneXpert machine; the spokes are surrounding Primary Health Care facilities or health service delivery points within 5 km radius. This intervention aimed at increasing access to GeneXpert assay for presumptive TB clients, effective result referral feedback mechanisms and increase TB notification across 14 states.

**Intervention or response:** A mixed model for sputum specimen transportation and Xpert result retrieval systems was established for courier transport using ‘Riders for Health’ across 156 ART facilities, PMVs, CPs and supported by Health Care Workers and ad-hoc staff in a “hub-and-spoke” model in 5 states.

The model developed adhered to an itinerary of mapped route to ensure sputum samples from presumptive TB patients were collected and transported from health facilities and communities, including patent medicine vendors and community pharmacists to GeneXpert sites for diagnosis and results retrieved back to requesting facilities.

**Results/Impact:** CTB project transported 153,610 samples over the 3-year period. In 2018 alone, 72,776 samples were transported demonstrating 3,892% increase over the 1,823 samples transported at baseline. A total 6,980 (9.6%) TB cases were detected from the total samples transported.

**Conclusions:** Adoption and strengthening of an effective sputum specimen transportation system greatly increased access to quality diagnostic services contributing to improved TB case finding. Despite low geographical coverage of GeneXpert machines in Nigeria, this mixed model approach has been adopted in the current Global Fund TB grant application as a key strategy to find and treat all missing TB patients.

### EP19-281-22 Lateral flow lipoarabinomannan test for diagnosis of TB amongst PLHIV in selected health facilities in Nigeria: hype or hope?

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**Background:** The high proportion of people living with human immunodeficiency virus (PLHIV) that died of tuberculosis (TB) in Nigeria and the low utilization of WHO-recommended rapid diagnostic (WRD) test for TB in 2018 necessitated the roll-out of LF-LAM for seriously ill PLHIV. We evaluated the effectiveness of LF-LAM for TB diagnosis in PLHIV across selected states in Nigeria.

**Design/Methods:** Nineteen ART facilities were utilized as study sites. Presumptive TB PLHIV with CD4 count of  $\leq 100$  cells/mm<sup>3</sup> or the seriously ill irrespective of CD4 count were enrolled between June and December 2019. Patients were tested for TB using both LF-LAM and Xpert or only LF-LAM where patients could not produce sputum or when test was inaccessible.

**Results:** Out of 642 persons screened, only 461 (72%) PLHIV that met inclusion criteria were enrolled. Of these, 306(66.4%) were female and 153 (33%) male. Age range was between 3 months and 84 years with a median age of 38 years. About 458 (99%) patients were tested with LF-LAM, 221 (48%) tested with both Xpert and LF-LAM and 240(52%) could not access Xpert test for some reasons. Detection rates for LF- LAM and Xpert were 24.5% and 20% respectively. Detection rate when both tests were combined was 33%. About 31(14%) patients would have been missed if only Xpert was used i.e. LAM positive, Xpert Negative, and 10 (4.5%) missed if LAM alone was used i.e. LAM negative, Xpert Positive, (pvalue= <0.001). Approximately 21% of patients who could not access Xpert test got diagnosed through LF-LAM.

**Conclusions:** The 31 (14%) additional cases of TB diagnosed that were LAM positive and Xpert negative could have been missed using Xpert alone and this demonstrated the additional benefit of LAM. Being a urine-based point-of-care- test, it bridged the diagnostic gap for PLHIV that could not produce quality sputum.

### EP19-282-22 Impact of the Rapid Molecular Test on the incidence of tuberculosis in an endemic city in the interior of São Paulo, Brazil

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**Background:** Tuberculosis, a communicable disease, is one of the 10 leading causes of death worldwide and the leading cause of death from a single infectious agent.

**Design/Methods:** Ecological study. The Prais-Winsten autoregression method was used to classify the time trend of the disease and then the Interrupted Time Series method was used to identify whether there was a change in incidence after the beginning of diagnosis using the Rapid Molecular Test (RMT).

**Results:** The temporal trend of tuberculosis in the municipality was classified as decreasing with a decrease of 18.1% per year (95%CI= -1.14 to -32.23) and also decreasing for tuberculosis in children under 15 years of age, with a decrease 6.9% per year (95%CI= -0.45 to -10.87). Pulmonary tuberculosis, resistant tuberculosis, extrapulmonary tuberculosis and TB-HIV co-infection were classified as stationary. Regarding the Interrupted Time Series, there was no change in level with the implementation of MRT in the municipality in relation to tuberculosis; however, a change is observed in the trend of resistant tuberculosis, being classified as increasing in the post-intervention period, that is, after the implementation of the MRT there was an increase of 0.6% per year (95%CI= 0.230 to 1.157) in the incidence of this condition in the municipality.

**Conclusions:** Evidence points to the impact of MRT in the detection of resistant tuberculosis, which a priori did not seem to be a problem in the scenario, the present study identified an increase in the rates of this condition after starting the diagnosis using the MRT; however, 3 years is a relatively short time to indicate the impact of technology in the context of sensitive tuberculosis, using conventional testing.



### EP19-283-22 Assessment of the quality management system in 23 national reference laboratories for tuberculosis in West and Central Africa using the SLIPTA tool

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**Background:** Apart from basic elements in quality control, National Reference Laboratories (NRLs) for tuberculosis (TB) in West and Central Africa rarely have a comprehensive quality management system in place. Thus, the performance of these laboratories is either weak and/or not maintained over time. In order to strengthen the capacities of these NRLs, the TB Lab project funded by the Global Fund against HIV/ AIDS, Tuberculosis and Malaria and coordinated by the WHO Supranational Reference Laboratory of Cotonou, was established.

**Design/Methods:** Thanks to this project, an assessment of 23 NRLs in this region was conducted between July 2019 and January 2020 using the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) checklist, a framework for improving quality of public health laboratories in developing countries to achieve the requirements of the ISO 15189 standard. Each NRL received the checklist at least two weeks prior to the assessment visit and was assessed by 2 auditors using this checklist.

**Results:** Among the 23 NRLs assessed, 18 obtained a score below 55% equal to 0 stars, 2 obtained a score between 55 and 64% (1 star), 2 obtained a score between 65 and 74% equal to 2 stars and 1 obtained a score of 86% equal to 4 stars. In the NRLs with 0 stars, 8 had no quality management system in place; fortunately, they are all motivated to set up this system.

**Conclusions:** The implementation of a quality management system in NRLs in West and Central Africa is heterogeneous with no comprehensive system in place in the majority of them. The quality improvement process in the SLIPTA framework provides a learning opportunity and pathway for continuous improvement, a mechanism for identifying resource and training needs, and a measure of progress. Support is planned within the project to improve the SLIPTA score of these laboratories.

### EP19-284-22 Results from Namibia's first TB national disease prevalence survey, 2017-2018

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**Background and challenges to implementation:** Namibia ranks among the thirty high TB-burden countries due to a high estimated incidence rate. The first countrywide TB prevalence survey was conducted in 2017 and 2018. We present the main findings from this survey.

**Intervention or response:** Sixty-eight clusters of 500 adult inhabitants each were sampled randomly after stratification by region and urban-rural setting. Following house-to-house listing of residents, eligible individuals were invited for TB screening, which included symptom interview and chest x-ray (CXR), followed by sputum testing for those who screened positive by symptoms or CXR. Sputum testing used Xpert MTB/RIF followed by smear microscopy and either culture or another Xpert MTB/RIF. Cases were defined as those with any positive culture result or a positive Xpert MTB/RIF with a compatible CXR.

**Results/Impact:** Household listing identified 56,922 individuals, whereas only 29,495 of the 38,353 (76.9%) eligible adults actually participated in the screening. 9,462 submitted sputum of the 10,884 that screened positive. 115 participants had positive first Xpert results, 52 had a positive culture result, 18 had positive central Xpert results and four had both a positive central Xpert and culture result. Overall, 138 participants had positive bacteriological results, and 123 satisfied the survey case definition. With multiple imputation and inverse probability weighting, the prevalence of bacteriologically confirmed TB in Namibia was determined to be 465/100,000 (95% CI, 340-590), with the prevalence rate twice as high in males (643/100,000; 95% CI 429-858) compared to females (304/100,000; 95% CI 196-413).

**Conclusions:** With 86.8% of the targeted sample size achieved, the demonstrated prevalence of TB in Namibia falls within the range previously estimated by WHO. The higher prevalence in males suggests a male-driven TB epidemic, as has been observed in other surveys. Targeted interventions need to specifically address TB in males, given both the high prevalence and their lower participation.

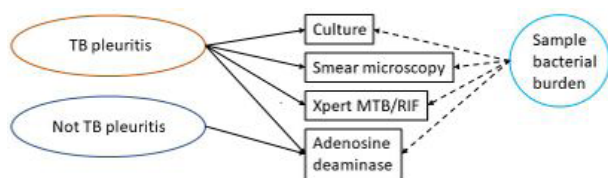
### EP19-285-22 Bayesian latent class analysis versus composite reference standards for assessing tuberculosis pleuritis diagnostic test accuracy

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**Background:** Tuberculosis pleuritis (TBP) is the most common form of extrapulmonary TB, representing 3-25% of the global annual TB burden, depending on the country. Prevalence estimates are highly uncertain as there is no reliable gold standard to definitively classify it. Despite recognition of the imperfect nature of employed reference standards, methods used to evaluate accuracy of new TBP tests, e.g. composite reference standards (CRS), do not account for the uncertainty in their accuracy. Consequently, existing estimates of TBP diagnostic test sensitivity and specificity are biased.

We used Bayesian latent class analysis (LCA) to estimate Xpert MTB/RIF (Xpert) accuracy for diagnosing TBP and compared these to estimates from multiple CRSs.

**Design/Methods:** An existing dataset of all adults presenting to a tertiary care hospital with suspected extrapulmonary TB in New Delhi, India, in 2012 was analysed. We selected individuals undergoing investigation for TBP with results for bacterial culture, smear microscopy, adenosine deaminase (ADA), and Xpert. A heuristic model was created to understand relationships between latent classes and tests, with a random effect to denote bacterial burden (Figure). A Bayesian approach was used to estimate the latent class model. The CRSs were defined by increasing numbers of positive component tests to estimate Xpert's accuracy. Analyses were performed using RJAGS (Version 4-8) through R-studio (3.5.2).



[Figure.]

**Results:** Using 388 patients with suspected TBP, TBP prevalence was 52.6% (95%CrI:47.6-57.6), and Xpert sensitivity and specificity were 29.7% (95%CrI:23.7-36.0) and 99.6% (95%CrI:97.8-100). Xpert sensitivity varied dramatically by CRS definition: sensitivity was 24% (95%CI:18-31) with a CRS of any one positive test result, increasing to 25% (95%CI:19-32) with two positive results, and reaching 100% (95%CI:77-100) with all four positive results.

**Conclusions:** Unlike CRS, Bayesian LCA produces accuracy estimates that incorporate reference standard uncertainty and conditional dependence for TBP, the most common form of extrapulmonary TB.

### EP19-286-22 A quarterly trend analysis of the contribution of the Wellness on Wheels intervention to TB case finding in Kano State, Nigeria

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**Background:** Of the estimated 429,000 new TB cases in Nigeria in 2018, only 120, 266 (24.8%) were notified. This gap is mainly due to under-diagnosis and under-reporting of detected cases. We analyzed the contribution of the Wellness on Wheels (WoW) intervention to case notification in Kano state, Nigeria over a period of 12 months.

**Background and challenges to implementation:** Of the estimated 429,000 new TB cases in Nigeria in 2018, only 120, 266 (24.8%) were notified. This gap is mainly due to under-diagnosis and under-reporting of detected cases. We analyzed the contribution of the Wellness on Wheels (WoW) intervention to case notification in Kano state, Nigeria over a period of 12 months.

**Intervention or response:** The WoW campaign was launched in Kano state on the 10th of April 2018. WoW is a mobile diagnostic unit (MDU) housing a digital X-ray machine & 2 four-module GeneXpert machines that deliver screening and diagnosis to the door step of the people at risk for TB aiming at same day diagnosis. Over a period of one year, screenings and diagnosis were conducted in slums across 12 local government areas, 4 prisons, markets and motor parks in the state. Results of the intervention were tabulated and analyzed as presented below.

**Results/Impact:** Over the one year period (Q2, Q3, Q4 2018 and Q1 2019); 68, 145, 193 and 203 TB patients, including 22(3.6%) RR-TB patients were notified by the WoW intervention. Over the same period, the Kano State TB and Leprosy Control Program (STBLCP) notified 1829, 2004, 2066 and 2023 TB patients bringing it to a total of 7922 patients over the four quarters. This represents an overall 2.9% increase in number of TB patients notified in the corresponding quarters of the preceding year (1766, 1905, 1929 and 2108). These increases are attributable to the WoW intervention as the Kano STBLCP would have had 5.1% decrease in case notification over the period, but for the WoW intervention.

**Conclusions:** Systematic screening using the WoW mobile diagnostic unit is an effective method of increasing TB case notification rate and should be replicated across other states. The government can key into the idea and procure additional mobile diagnostic units for sustainability and ownership.

## EP19-287-22 ARREST-TB: Accurate, Rapid, Robust and Economical diagnostic Technologies for Tuberculosis

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**Background:** Tuberculosis (TB) is the leading cause of death from infectious diseases, costing ~1.5 million lives per annum. However, WHO has estimated that only half of all TB cases are diagnosed and reported, with, alarmingly, only 25% of drug-resistant TB cases identified and notified (2016).

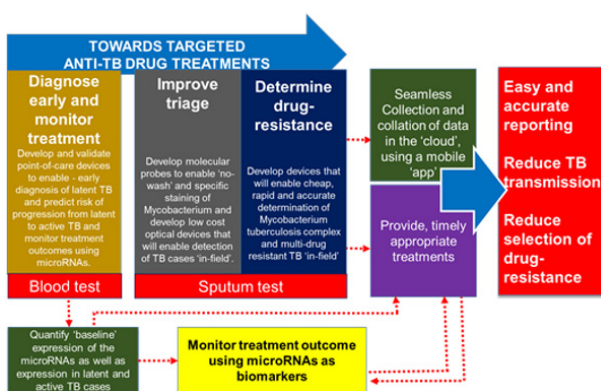
This is caused partly due to poor access to appropriate diagnosis, as most of the current 'gold standard' diagnostic tools are simply too expensive and ill-adapted to resource-limited settings.

Here we aim to present how our multilateral project, ARREST-TB, is aiming to address these issues.

**Design/Methods:** ARREST-TB is a multi-disciplinary consortium of academic institutes, research organisations and industries from the UK, Italy, Spain, Russia and India, developing a suite of TB diagnostics solutions, with the European partners working closely with, and conducting evaluation/validation studies in Russia and India.

For further information, see: [www.arrest-tb.net/](http://www.arrest-tb.net/); [www.chem.ed.ac.uk/news-events/news/university-edinburgh-leads-way-tb-diagnostic-technologies](http://www.chem.ed.ac.uk/news-events/news/university-edinburgh-leads-way-tb-diagnostic-technologies). Our key deliverables are (summarized in the figure):

- Rapid screening of TB infection and drug resistance profiling
- Rapid molecular profiling of drug resistance
- Biomarkers and point-of-care devices for early TB diagnosis and assessing treatment response



[Figure.]

**Results:** We will share an overview of the results of low-cost technologies developed by ARREST-TB.

As examples:

- 'triage tests' using molecular probes that will specifically stain Mycobacterium in sputum
- scalable molecular diagnostic platform for use even in remote locations with low operator skills.

**Conclusions:** We will show the significant progress made by ARREST-TB towards providing diagnostic solutions with negligible implementation costs, significantly lower running expenses, and minimal expertise for operation than current technologies, while taking TB-testing to the patients 'in-field' to enable active case-finding. These tests will allow rapid, low-cost detection of TB/Multi-drug resistant-TB with a mobile app to allow interpretation of results, with log in details of the location, as well as transmission of the data for collation and reporting, to help reduce under-reporting of TB.

## ABSTRACT PRESENTATIONS FRIDAY 23 OCTOBER 2020

### ORAL ABSTRACT SESSION (OA)

#### OA-22 Improving the quality of care

##### OA-22-633-23 Enhancing early detection of tuberculosis through targeted outreaches in hotspots: an experience of Amref Health Africa in Kenya

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**Background and challenges to implementation:** Tuberculosis (TB) is a disease of major public health concern. People with active TB can infect 5–15 other people through close contact over the course of a year. WHO promotes preventive action through early screening and treatment for active TB by promoting access to universal health care among other strategies. Among the key interventions identified and prioritized in the Kenya National TB Strategic Plan (2019 – 2023) is targeted community based TB screening in areas of focalized transmission within the community.

**Intervention or response:** Amref Health Africa in Kenya in collaboration with National TB program carried out targeted outreaches between January 2018 and March 2020 in 10 counties. County TB coordinators identified areas which reported high TB persons for targeted outreach services. These included; schools, prisons, Health Facilities, Market places, and public transport termini. Community mobilization, sensitization and health education on Tuberculosis was undertaken by community health volunteers and Public Health officers. This was by using public address systems and door to door visits. During the outreach, health education and symptomatic Tuberculosis screening was done by health care workers from local health facilities. Chest X-rays were taken for presumptive persons who consented. Sputum samples were collected for those whose X-rays were suggestive of Tuberculosis for GeneXpert testing.

**Results/Impact:** Eleven outreaches were conducted where 33443 people were screened for Tuberculosis. Of these 25% (8,227) were presumed to have Tuberculosis,

among whom 79% (6475) had chest X-Rays done. Of these, 43% (2938) had their sputum samples further evaluated using Gene expert. A total of 154 tuberculosis cases were identified, 52 based on X ray results while 102 through Gene expert. All the 154 were initiated on treatment.

**Conclusions:** There are still people in the community who are missed with signs and symptoms of Tuberculosis and outreaches are a recommendable way of reaching them.

##### OA-22-634-23 A precision public health approach to identify at-risk population segments and their drivers for not seeking care for tuberculosis

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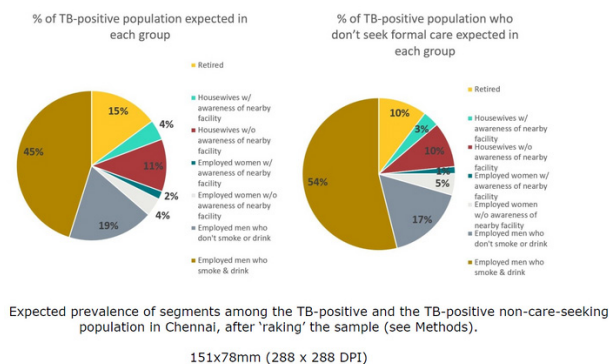
**Background:** Delaying to seek care for tuberculosis (TB) leads to worse treatment outcomes and greater spread. To reduce delays, it is essential to identify comprehensive barriers to prompt care-seeking and target populations most at risk of this behavior. Previous work has identified such drivers only in people captured by the health system, often long after initial care-seeking.

**Design/Methods:** We conducted a community-based survey of 84,625 households in Chennai, India, to identify 1,667 people with TB-suggestive symptoms in 2017-18. We then followed individuals prospectively to observe care-seeking behavior. We used a comprehensive survey to identify contextual and perceptual drivers of care-seeking, then performed multivariate analyses to identify predictors of prompt care-seeking. To identify profiles of individuals most and least at risk to delay care-seeking, and their underlying barriers, we segmented the sample using unsupervised clustering. Finally, we estimated the percent of the population with TB that would fall into each segment.

**Results:** Characteristics of delayed care-seeking include smoking, drinking, being employed, preferring different facilities than the community, believing to be at lower TB risk than others, believing TB is common, and specific symptom characteristics. Clustering analysis re-



vealed seven population segments that differed in care-seeking behavior, ranging from a retired/unemployed/disabled cluster where 70% promptly sought care to a small cluster of employed men who problem drink and smoke, where only 42% did so. While the latter segment only made up 10% of the sample, modeling showed that they account for roughly 45% of individuals with TB and 54% of individuals with TB who delay care-seeking.



[Figure.]

**Conclusions:** Employed men who problem drink and smoke are a prime target for interventions to increase care-seeking, and reducing delays in this group could dramatically reduce the spread of tuberculosis. Specific interventions could address a lack of time and convenience.

### OA-22-635-23 Implementing the standardised patient method to evaluate quality of TB care among private practitioners in South Africa

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**Background and challenges to implementation:** TB remains the leading cause of mortality in South Africa and nearly 30% of South Africans with TB-related symptoms first present to private general practitioners (GPs). However little is known about the quality of TB care received from GPs. We evaluated the feasibility of utilising patient actors (Standardised Patients [SPs]) to determine the quality of TB care amongst private GPs in Durban and Cape Town.

**Intervention or response:** A project team comprising TB and quality-of-care experts, epidemiologists, social scientists, and GPs was assembled. GP professional bodies and independent practice associations (IPAs) were consulted. Sixteen SPs were trained in three TB case presentations and coached to remain passive in consultations to avoid biasing quality outcomes. Pilot testing was undertaken to ensure standardisation and recall. Eligible GPs, identified from online listings and community drive-throughs, were consented to receive up to three SPs unannounced over a six-month period, and contacted thereafter to determine rates of SP detection. Standardised surveys and interviews were conducted with a sub-sample of GPs to measure knowledge and practice gaps and provide context. Continuous Professional Development events were held to disseminate findings.

**Results/Impact:** In total 221 (58%) of 384 GPs consented (Durban=54%, Cape Town=61%). While multiple visits to consenting GPs slowed implementation, support from IPAs, emphasis on provider anonymity, and commitment to dissemination aided recruitment. Overall, 510 SP consultations, 50 knowledge surveys, and 30 interviews were successfully met over 10 months. The SP detection rate was 2%. Cases were correctly managed in 56% of consultations (Durban=42%, Cape Town=68%).

**Conclusions:** The SP method was feasible and accepted for evaluating the quality of TB care amongst private GPs in urban South Africa. IPA endorsement and results dissemination facilitated provider engagement. Although quality of care was lower than expected, there was interest in ongoing SP assessment in both public and private sectors.

### OA-22-636-23 Using low-cost interventions to improve availability of tuberculosis medicine in Uganda

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**Background and challenges to implementation:** Availability and uninterrupted access to tuberculosis (TB) medicine are a challenge in Uganda. A baseline assessment in 2018 indicated frequent stockout of TB medicines at health facilities. These stockouts were attributed to stockouts experienced at the central warehouse due to global stockout of Rifampicin Active Pharmaceutical Ingredient, a low order submission rate (40%) from sites to the central stores, poor quantification, and poor inventory management (50%). The unavailability of prescribed medicines compromised treatment outcomes and the quality of TB care.

**Intervention or response:** To improve TB medicine availability, USAID Defeat TB project supported the implementation of a TB medicines web-based order-

ing and reporting system (TWOS). The implementation included training 108 facility TB focal persons, 25 district health staff, and 32 central warehouse staff on how to properly use the TWOS. The system was piloted for three months in 152 sites. The project made phone calls and sent daily SMS reminders to sites the week before order deadlines. The districts held order review meetings, and conducted on-site mentorship on inventory management using a quality improvement approach. The districts were trained to use monthly stock-status dashboards to inform medicine redistribution.

**Results/Impact:** Between October 2017 and December 2019, timeliness of orders submitted to the central warehouse improved from 40% to 90.4%. TB medicine availability at health facilities increased from 75.5% to 87.7%.

Additionally, facilities with no stockouts of tracer TB drugs improved from 59% in to 93%. The lead time reduced from 60 to under 30 days and the quality of submitted orders improved. Fewer medicine expiries were also reported.

**Conclusions:** The package of interventions, including SMS reminders, web-based ordering, stock-status dashboards, order review meetings, and coaching helped to improve the availability of TB commodities at the targeted health facilities. These low-cost interventions should be applied in settings that face similar challenges to ensure TB commodity security.

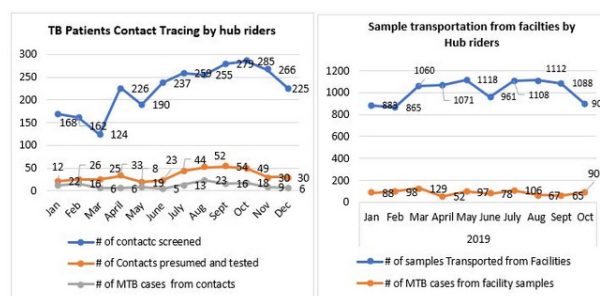
### OA-22-637-23 How the dual role of community facilitators as sample transporters and tuberculosis patient contact tracers increased contacts coverage and TB case finding in Kampala

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**Background and challenges to implementation:** The laboratory network in Uganda is linked by motorcycles transporting samples from lower health facilities to hubs. Hubs are referral laboratories serving 30 facilities within a 40 km radius. In 2018, 21 laboratories with genexpert machines served 1,458 public and private facilities in Kampala. The 2015 Uganda Tuberculosis prevalence survey highlighted inadequate systems for TB patient contact tracing in the community contributing to missing TB cases. Challenges to timely TB diagnosis included limited accessibility to communities and delays in reaching contacts of TB patients to facilities. To address these ,USAID Defeat TB project integrated the sample transportation system with community TB contact tracing.

**Intervention or response:** The USAID-funded Defeat TB project procured motorcycles for three community linkage facilitators (CLFs) already stationed at laboratory hubs to transport samples throughout Kampala. The CLFs served a dual role, transporting samples for genexpert testing and tracing contacts of TB patients. Daily routine included retrieving test results and lists of patients whose contacts needed to be screened, retrieving samples from 83 lower-level facilities, visiting TB contacts in the community to screen them for TB, and collecting sputum samples.

**Results/Impact:** Number of TB patients contacts screened improved by 66% from January to October 2019. The number of presumptive TB cases identified from TB contacts increased more than 100% between January to October 2019. Number of samples transported from lower facilities improved by 23% from January to September 2019. The number of TB cases from community TB contacts and samples from lower-level facilities improved by 33% between January to October 2019, and by 20% from January to July 2019, respectively.



[Figure. Tuberculosis patient contacts coverage and sample transportation in Kampala]

**Conclusions:** CLFs' dual role of transporting samples and conducting community TB contact tracing effectively improved access to genexpert tests and TB case finding. The integration of these two services can be scaled up to other districts to increase TB cases finding.

### OA-22-638-23 Quality of TB and HIV care among private general practitioners in two South African cities

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**Background:** The private sector may be vital in detecting undiagnosed TB and TB-HIV in South Africa, where nearly 30% of people with TB symptoms first seek care. From 2018-2019, we measured quality of TB and HIV care received by patient actors, known as standardised patients (SPs), who presented to private general practitioners (GPs) in Durban and Cape Town.

**Design/Methods:** Sixteen SPs (eight per city) were trained in one of three case presentations: classic TB symptoms (cough, fever, weight loss, night sweats), HIV-positive on probing (SP1); classic TB symptoms with positive GeneXpert laboratory report, HIV-negative on probing (SP2); and classic TB symptoms with history of incomplete TB treatment, HIV-positive on probing (SP3). Private GPs in high TB burden communities were identified via mapping and online listings, and approached for consent to receive up to three unannounced SPs over six months. A standardized survey was administered to SPs after each interaction to measure quality of care. Correct management was defined as i) test or referral for TB or HIV or ii) referral to a public facility.

**Results:** In total 213 consenting GPs (27% female, 84% trained in-country) participated in 510 (Durban=210, Cape Town=290) interactions with ≥1 SP. Overall, TB was managed correctly in 64% of interactions: SP1=45%, SP2=85%, and SP3=69%. HIV was managed correctly in 58% of interactions: SP1=41%, SP2=76%, and SP3=61%. The Table describes quality of care measures by city.

**Conclusions:** Private GPs correctly managed TB-related symptoms more often when accompanied with microbiological confirmation or a history of TB diagnosis. Correct practices were associated with improved inquiry into symptomology and dispensation of fewer medications.

More Cape Town providers managed TB and HIV correctly. Findings suggest an opportunity to engage the private sector in early diagnosis of TB and HIV care, and referral to the public sector.

		Overall (n=510)	SP1 (n=201)	SP2 (n=157)	SP3 (n=152)
Correct TB management	Durban	54%	33%	80%	63%
	Cape Town	73%	56%	87%	75%
Correct HIV management	Durban	45%	31%	62%	51%
	Cape Town	68%	51%	83%	70%
Queried ≥3 of 4 symptoms	Durban	50%	48%	56%	48%
	Cape Town	67%	66%	70%	62%
Medications dispensed* (x̄)	Durban	3.9	4.3	3.0	3.8
	Cape Town	2.5	3.1	1.8	2.7

Blue text indicates significant difference between cities at p<0.01  
\*includes prescriptions

[Figure. Quality of care by city and case description]

### OA-22-639-23 Understanding the dynamics of antibiotics and steroids prescription prior to TB diagnosis in South Africa's private sector

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**Background:** Unnecessary prescription of medication has been noted in quality-of-care studies in India, China, and Kenya. Antibiotic and steroid use can lead to TB diagnostic delay and/or complications with TB treatment. To gain insight into prescription dynamics of general practitioners (GPs), we embedded a qualitative sub-study into a quality of TB care study among private GPs in an urban centre of South Africa.

**Design/Methods:** In the parent study, quality-of-care measures were captured over 220 consultations between 96 consenting GPs and eight patient actors. Actors were trained as standardised patients (SPs) in three typical TB case presentations involving a 2-3 week cough. SPs were coached to be passive in consultations to avoid biasing providers' practices or decisions. In-depth interviews were subsequently held with 15 GPs who, in addition to having dispensed/prescribed at least one antibiotic or steroid at each consultation (n=36), were selected to achieve maximum variation by age, sex, ethnicity, and location. Interview transcripts were analysed utilising content analysis.

**Results:** Interviews uncovered novel determinants of prescribing practices. Among other diagnoses, GPs reported providing antibiotics and/or steroids when suspecting cough-based conditions like bronchitis, chronic pulmonary disease, and allergies following clinical evaluation. GPs described that patients commonly prefer the private sector when seeking expert medical advice and/



or medications. Participants described feeling pressure to dispense medications, regardless of condition. While most GPs were adamant about resisting such pressure, some admitted to yielding to expectations. GPs reported utilising various strategies to mitigate unnecessary prescription, such as: affirming the doctors' role as expert; explaining futility or potential harm of medication; or providing what they deemed innocuous medication (e.g. panado, cough syrup).

**Conclusions:** Findings suggest that unnecessary antibiotic and/or steroid prescription to patients presenting with TB symptoms in the private sector may result from perceived patient expectations and/or attempts to treat cough symptoms more broadly.

## OA-23 TB: finding the missing millions

### OA-23-640-23 Improving detection of persons with Tuberculosis during National Polio Immunization Plus Days and Polio Outbreak Response activities in Kaduna State, Nigeria

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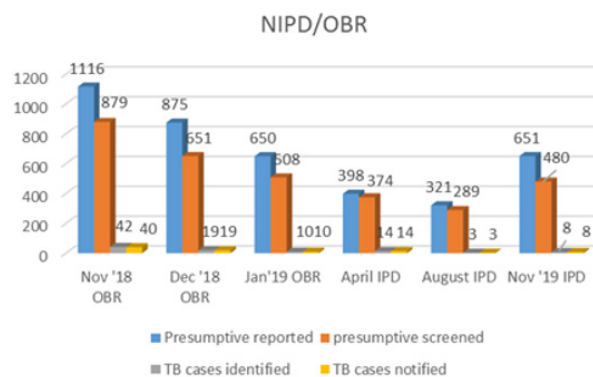
**Background and challenges to implementation:** Nigeria accounts for 8% of the missing/undiagnosed persons with TB globally with over 300,000 missing cases. TB case detection is very low in Kaduna State (only 22% of estimated persons with TB diagnosed, accounting for about 5% of all missed persons with TB in Nigeria).

This intervention leveraged house-to-house polio vaccination teams during the National Immunization Plus days (NIPD) and other polio-virus outbreak response (OBR) activities to improve TB detection in Kaduna state.

**Intervention or response:** The intervention began in November 2018. An average of 50,000 (10%) households are selected and visited in each of the 23 Local Govern-

ment Areas (LGAs) of the state. House-to-house polio vaccination teams identified persons with cough of two weeks or longer (presumptive TB) in the household and community while vaccinating and screening for acute flaccid paralysis. Local government TB supervisors and their teams followed up the presumptive patients identified, collect specimen and test them using the national TB testing algorithm.

**Results/Impact:** In six (6) rounds of NIPD/OBR campaigns lasting 4 days each between November 2018 and November 2019, 4011 presumptive TB patients were identified. Of these, 79.3% (3,181) were tested; 3% (96) were diagnosed with TB (66% Male and 33% Females with mean age of 36 years, 7% were children less than 15 years). 98% (94) of the diagnosed persons with TB were traced, and enrolled on treatment. One patient could not be traced and one died before notification. This result accounted for about 3% of all persons with TB notified in Kaduna state from November 2018 to November 2019 and 10% of persons with TB reported through active case finding in 2019.



[Figure.]

**Conclusions:** The approach, if scaled up to cover the entire state and house-to-house teams empowered to collect specimen on the spot from identified presumptive and transport it for testing, can improve TB case detection in Nigeria

### OA-23-641-23 Results of Active Case Finding (ACF) without and with the joined approaches with the Seed-and-Recruit model

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**Background and challenges to implementation:** A mobile mass screening using a one-off ACF approach was conducted to find missing cases of tuberculosis (TB) in Cambodia. Comparison of the results of ACF alone and

the joint approach with seed-and-recruit model to improve tuberculosis case detection and linkage to treatment.

**Intervention or response:** The mobile ACF approaches were conducted among elderly aged 55 and over and any community member with a TB symptom(s) was encouraged to receive a chest x-ray and Xpert MTB/RIF test. The two models of ACF without (model A- in 2017) and with (Model B-in 2019) joint approaches with seed-and-recruit models were conducted at different 126 and 146 health facilities within the 2 years interval of these two models.

**Results/Impact:** A model A, mobile ACF screened 53,098 individuals by CXR and tested 9705 by Xpert MTB/RIF Ultra with 777 Bac+ and 2801 all form TB cases while a model B screened 50,720 by CXR and tested 6514 with 657 Bac+ and 2,303 all forms of TB cases. The model A, new Bac+ increased +164% for all ages and +168% for all form of TB cases while model B has new Bac+ increased +161% and +219% respectively compared with expected trend three years post-intervention notifications. Treatment success rates improved in all operational districts if compared with model A.

**Conclusions:** A significant increase in both models can be observed from the results while the trend expected going down every year. These models have demonstrated their efficiency in finding missing cases by incorporating active approaches. By bringing the screening equipment to the field to increase coverage, combined approaches such as this could be used to reduce a backlog of untreated, prevalent TB.

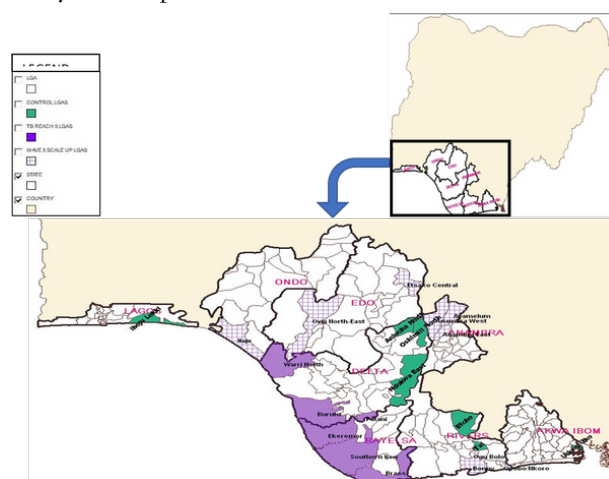
**OA-23-642-23 Missing no more: Improved case detection of childhood TB through active case-finding in hard-to-reach riverine communities in Southern Nigeria**

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**Background and challenges to implementation:** Childhood Tuberculosis (TB) accounts for one-tenth of global TB burden yet, it remains under-diagnosed, under-reported, and under-treated. For 10years, Nigeria has annually reported 6-8% as against WHO's estimated 10-20% child proportion in high-burden countries. Paediatric TB diagnosis is difficult with sputum-based assays as the uneasy task of producing sputum is compounded by the specimen being pauci-bacillary. This impasse necessitates a dependence on clinical diagnosis.

DAHW-German Leprosy and TB Relief Association implemented a project grant funded by the Stop TB Partnership initiative, TB REACH Wave 5 Scale-Up in hard-to-reach communities of southern Nigeria.

**Intervention or response:** The project was implemented in 15 purposively selected Local Government Areas (LGAs) in 6 states with perennially low TB case notification. Seven (7) LGAs in 4 states served as control. Interventions include advocacy visits to stakeholders: State, LGAs and community gatekeepers. Demand creation through community sensitization, health outreaches (Chest Camps) for immediate screening for presumptive TB was done by Community Volunteers and we established a sputum transport mechanism. Children were transported to access free but distant chest X-ray services provided by The Global Fund. Financial incentives were offered to motivate case-finding and case-holding. Training of medical doctors in those LGAs on clinical diagnosis of childhood TB was reinforced quarterly through joint clinical reviews with radiologists/paediatricians. Clinical diagnosis was based on the NTP's criteria. Data notified (July-2017 to December-2019) was analysed and presented.



[Figure.]

**Results/Impact:** Total childhood TB proportion increased from 4% (30/ 740) to 21% (347/1657) in intervention areas. Clinically diagnosed cases were 278(80%), with 51% (177/347) below 5years. Childhood TB yield was a 10.6-fold increase from baseline, and 8 times the control LGAs.

**Conclusions:** Robust community-wide interventions together with enablers to improve case-finding holds strong promise to finding missing childhood TB cases in hard-to-reach areas.

### OA-23-643-23 Thinking outside the (TB) box: Intensified pediatric-TB case-finding in non-TB entry points in nine sub-Saharan countries

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**Background:** Children and adolescents aged 0-14 years access health care through a variety of facility-based settings. TB screening is seldom performed during these medical encounters and presumptive TB case identification and subsequent diagnostic capacity are limited. To address the screening and diagnosis gap, we implemented an intensified, facility-based pediatric TB training program and evaluated systematic pediatric TB screening in various non-TB entry points of health facilities across nine sub-Saharan countries.

**Design/Methods:** 198 health facilities were purposively selected across nine countries (Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Kenya, Lesotho, Malawi, Tanzania, Uganda, and Zimbabwe). We delivered comprehensive, facility-based pediatric TB training to health workers and introduced systematic TB screening for all clients under 15 years of age attending outpatient departments (OPD), pediatric wards, maternal and child health (MCH), nutrition, HIV, and other relevant, non-TB-specific child health services. Screening data were prospectively collected between December 2018 to December 2019 using project forms. Children with at least one TB symptom were identified as presumptive TB cases and referred for investigations and diagnosis. Descriptive statistics were used for proportions.

	MCH	OPD	Pediatric Ward	Nutrition	Others	Total
# Screened	271,816 46%	279,960 47%	26,859 4%	10,642 2%	8,044 1%	597,321 100%
% Presumptive TB identified	0.3% (745/271,816)	2.1% (5,843/279,960)	5.4% (1,450/26,859)	1.7% (178/10,642)	12.7% (1,025/8,044)	1.5% (9,241/597,321)
% Diagnosed among presumptive TB	15.7% (117/745)	27.2% (1,589/5,843)	27.9% (404/1,450)	37.6% (67/178)	17.5% (179/1,025)	25.5% (2,356/9,241)
# Needed to screen to identify one TB case (NNS)	2323	176	66	159	45	254
Entry point contribution in TB case finding	5.0% (117/2,356)	67.4% (1,589/2,356)	17.1% (404/2,356)	2.8% (67/2,356)	7.6% (179/2,356)	100.0% (2,356/2,356)

[Table 1: Pediatric case detection among various facility entry points]

**Results:** Overall, 597,321 children were screened, enabling the identification of 9,241 presumptive and 2,356 diagnosed TB cases. Among all presumptive TB identified, 81% (7,471/9,241) were identified in OPD, pediatric ward, and nutrition entry points combined, jointly contributing to the diagnosis of 87% (2,060/2,356) of all TB cases among non-TB entry points. Overall, 154 children were needed to be screened (NNS) to find one TB case across those three entry points combined.

**Conclusions:** The NNS to diagnose one case of pediatric TB in certain non-TB entry points was low, suggesting these entry points should be prioritized for pediatric TB case finding. National programs should consider implementing systematic and pediatric-specific TB symptom screening in triage/waiting of non-TB entry points to increase pediatric case finding in high burden countries.

### OA-23-644-23 Implementing structured TB screening as part of routine child care services at orphanage homes in a Nigerian Local Government Area

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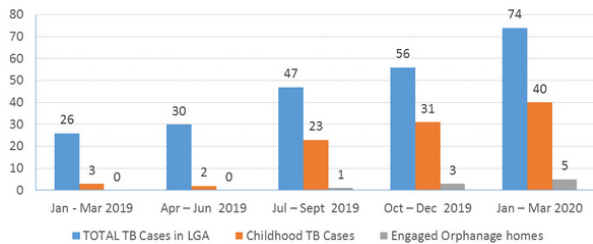
**Background and challenges to implementation:** According to the latest National Demographic and Health Survey, 6% of all Nigerian children aged 0-18 are orphans. With a rate of 9%, the south-east zone, where this intervention was conducted, has the highest proportion of orphaned children in the country. Orphans are usually exposed to an intersection of disadvantages some of which are risk factors for TB such as malnutrition and poor or overcrowded living conditions.

The objective of this intervention was to enhance diagnosis of childhood TB through a systematic engagement of orphanage homes in Ogbaru local government area (LGA) of Anambra state, to offer routine TB screening and testing to the children and caregivers.

**Intervention or response:** Five orphanage homes within Ogbaru LGA were selected and engaged for this intervention. Thereafter, TB outreaches were carried out in phases in each orphanage home with key activities including training of the caregivers on routine TB screening using the National algorithm for paediatric TB clinical screening. Sputum samples were collected from the children and caregivers showing signs and symptoms. Children who were unable to expectorate were referred to paediatricians for further review and investigations.

**Results/Impact:** Over the 9 months of this intervention, a total of 688 persons (371 children; 239 caregivers; 78 other staff) were clinically screened for TB (monthly) across the five homes. 526 presumptives were identified

(325 children and 201 adults). A total of 61 confirmed TB cases were identified amongst the orphaned children and 27 amongst caregivers and staff. The proportion of Childhood TB cases reported by the LGA increased from 8% pre-intervention average to 53% during the intervention period.



[Figure. Five quarter trend of TB cases in Ogbaru LGA and number of orphanage homes engaged]

**Conclusions:** Routine systematic TB screening for children living in orphanage homes should be considered a critical component of their care. It serves to interrupt the spread of TB in such closed vulnerable population and portends better life chances for the children.

**OA-23-645-23 Data-driven tuberculosis active-case finding in South Kivu, DRC, leveraging innovative predictive and surveillance reporting software applications**

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**Background and challenges to implementation:** The WHO recommends performing active-case finding for tuberculosis when the incidence rate surpasses 1%. This threshold is not attained nationally even for high-burden countries. New tools are necessary to identify pockets of high tuberculosis incidence.

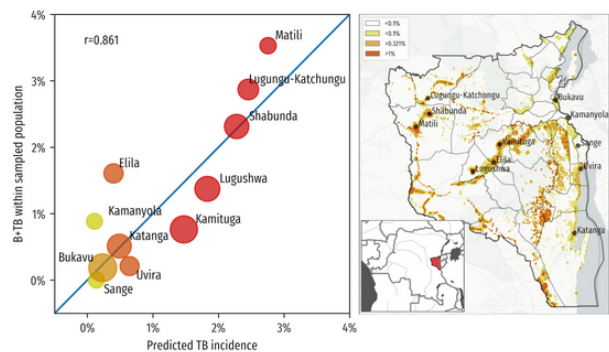
**Intervention or response:** We designed a data-driven approach for tuberculosis active case finding. First, we identified local communities at high risk of tuberculosis

by designing maps that leverage openly available data and tuberculosis notification reports to predict the incidence rate.

Second, we determined the risk scores of individuals screened from door to door by conducting case finding missions using Mediscout© web and mobile apps. The latter has a questionnaire that evaluates the risk of screened persons using a scoring system evaluating symptoms and exposure to TB.

**Results/Impact:** We trained 20 community health workers that screened 13,841 persons in 11 locations of South Kivu; 5 were classified as high-risk by the prediction incidence maps. Using the MediScout risk questionnaire, 7,437 persons were referred for a test. Of those referred, 1,150 presented for a test; 770 from high risk, while 383 from low-risk areas. 112 (9.7%) were confirmed positive in a Ziehl-Neelsen microscopy test. In high-risk locations, 91 were confirmed positive (1.6% of the screenings), while in low-risk areas, only 21 were positive (0.25% of the screenings). The community and individual risks correlate with the confirmed cases (pearson=0.861 and 0.836 respectively).

**Conclusions:** These results indicate that a better knowledge of the incidence rates is a key factor for identifying priority communities with a higher incidence rate than the threshold of 1% recommended by the WHO. In these locations, the triage capabilities of the Mediscout© apps let us perform less than 50 screenings and 9 microscopy tests to find a single case.



Left- Percentage of laboratory-confirmed cases in each of the screening sites plotted against the predicted incidence rate. Right- incidence rate prediction map for the province of South Kivu (DRC) showing all screening sites.

[Figure.]



### OA-23-646-23 Finding missing patients: yield of targeted universal testing for tuberculosis in high-risk groups presenting to 30 primary health care facilities in South Africa

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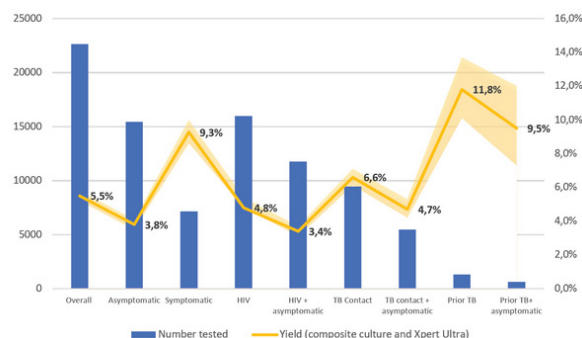
**Background:** Globally, TB control programmes use symptom-based screening to identify individuals for further investigation. However, recent data suggests that this does not find all patients with TB.

**Design/Methods:** The Targeted Universal Testing for Tuberculosis (TUTT) study is a cluster-randomized trial evaluating the effectiveness of a risk-factor based laboratory screening intervention in 60 primary health care facilities in South Africa. In 30 intervention clinics, adult clinic attendees with  $\geq 1$  TB risk-factor – HIV infection; recent contact with a TB patient; recent prior TB – were tested irrespective of reported symptoms. A single spontaneously expectorated sputum sample was split after centrifugation for Xpert Ultra and liquid mycobacterial culture. We describe the yield of Mycobacterium tuberculosis (MTB) detection in these targeted risk groups. Xpert Ultra trace results are excluded from these findings.

**Results:** 22,638 participants (62% female; median age 39 years (IQR:27-49); 70% HIV positive) were included; 1256 (5.5%, 95% CI:5.2–5.8%) were positive for MTB by Xpert Ultra and/or culture. Concordance between positive Ultra (excluding trace) and positive culture was 82% (547/668) however most Ultra-trace results were culture-negative (88%; 316/360). By risk group, yield was 4.8% in HIV-infected adults (95% CI:4.5–5.2%); 6.6% in those with a recent TB contact (95% CI:6.1–7.1%); and 11.8% in people with prior TB (95% CI:10.1–13.7%). Overall, 47% of MTB identified was in individuals reporting no symptoms of TB. In this group, 3.8% (591/15433; 95% CI:3.5–4.1%) were positive for MTB; 3.4% (95% CI:3.0–3.7%) in the HIV-infected group; 4.7% (95% CI:4.1–5.3%) in recent TB contacts; and 9.5% (95% CI:8.7–14.3%) in those reporting prior TB.

**Conclusions:** The overall yield of targeted risk-factor-based testing was high (5,500/100,000), even in the absence of symptoms (3,800/100,000). This approach finds

individuals with MTB beyond symptom-based testing. Further research is required to assess whether TUTT contributes to reducing: TB transmission, morbidity, and mortality.



[Figure. Yield of targeted risk factor based testing for tuberculosis in three high risk groups]

### OA-24 TB and diabetes

#### OA-24-647-23 High proportion of transient hyperglycemia at tuberculosis diagnosis among people living with and without HIV in South Africa

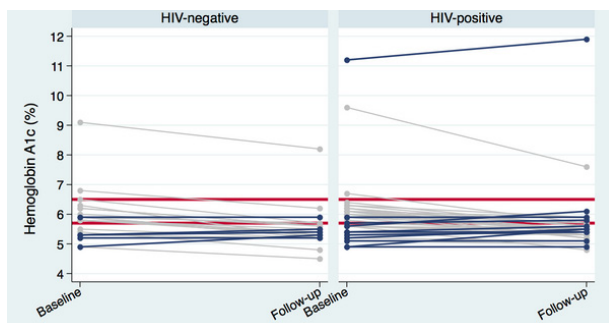
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**Background:** Diabetes mellitus and HIV are each associated with poor tuberculosis treatment outcomes. Hyperglycemia detected at the time of tuberculosis diagnosis may be transient, though it is unclear whether this varies by HIV status.

**Design/Methods:** We performed a prospective cohort study (Regional Prospective Observational Research in Tuberculosis [RePORT]) of adults treated for culture-confirmed, drug-susceptible tuberculosis at the KwaDabeka tuberculosis clinic in Durban, South Africa from 2016-2019. We measured hemoglobin A1c (HbA1c) at tuberculosis diagnosis (baseline) and HbA1c, fasting

insulin, and fasting glucose 12-15 months after tuberculosis diagnosis (follow-up). We compared baseline and follow-up HbA1c using the Wilcoxon signed-rank test and compared follow-up homeostatic model assessment of insulin resistance (HOMA-IR) by HIV status using the Wilcoxon rank-sum test. We used logistic regression models to test associations with hyperglycemia (HbA1c  $\geq 5.7\%$ ) at follow-up.

**Results:** Of 100 adults enrolled in the study, 62 had culture-confirmed, drug-susceptible pulmonary tuberculosis with baseline and follow-up data. Of these, 40 (65%) were male, 39 (63%) were HIV-positive, and median body mass index (BMI) was 20.8 kg/m<sup>2</sup> (interquartile range [IQR] 18.6, 22.7). Six (10%) individuals had baseline HbA1c  $\geq 6.5\%$  (including 3 with previously diagnosed diabetes), and 33 (53%) had baseline HbA1c 5.7-6.4% (none with previously diagnosed diabetes). Median HbA1c decreased from 5.9% (IQR 5.4, 6.1%) at baseline to 5.5% (IQR 5.3, 5.6%) at follow-up ( $p < 0.001$ ). This was similar for HIV-positive and HIV-negative participants (Figure). HOMA-IR (median 1.4 [IQR 1.0, 2.2]) did not differ by HIV status. Fifteen (24%) individuals did not resolve hyperglycemia (HbA1c  $\geq 5.7\%$  at follow-up); HIV status was not associated with lack of hyperglycemia resolution (odds ratio 1.32; 95% confidence interval 0.37, 4.66) when adjusting for sex and BMI.



[Figure. Hemoglobin A1c (HbA1c) at baseline and at 12 - 15 months after diagnosis and starting treatment (follow-up) for drug-susceptible culture-confirmed tuberculosis according to HIV status at baseline. Horizontal red lines denote HbA1c levels of 5.7% and 6.5% for reference. Gray lines denote decreased follow-up HbA1c; blue lines denote increased or equal follow-up HbA1c]

**Conclusions:** Most study participants had hyperglycemia at baseline. Although median HbA1c decreased by 12-15 months after tuberculosis diagnosis and did not differ by HIV status, hyperglycemia persisted in 24% of individuals.

### OA-24-648-23 A systematic review on the effect of diabetes mellitus on the pharmacokinetics of first-line tuberculosis drugs

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**Background:** Coexistence of DM with TB is associated with a 4-fold increased risk of treatment failure and 2-fold increased risk of death. In addition, TB-DM patients have a higher bacterial burden, delayed sputum culture conversion, more extensive lung disease, and a greater risk of developing drug resistance. DM may affect kidney function, gastric emptying and many other biochemical pathways that are involved in drug metabolism. To better understand the influence of pharmacokinetics (PK) in this population, we performed a systematic review on the effect of DM on PK of anti-TB drugs. **Design/Methods:** PRISMA guidelines were followed. Medline and EMBASE were searched from 1987 to December 2019. All peer-reviewed original research articles describing pharmacokinetics of anti-tuberculosis drugs in DM patients were included.

**Results:** Of the 140 records that full-filled inclusion criteria, we identified 15 studies that assessed the PK of anti-TB drugs among patients with DM. Twelve measured rifampicin plasma concentrations and of those, seven demonstrated up to 50% lower total rifampicin exposure and peak concentrations among diabetic patients. While the remaining five studies did not indicate any difference in rifampicin plasma concentrations among DM patients, there were significant heterogeneity and potential biases that might have influenced the results. Of seven studies that measured isoniazid (INH) PK, six studies demonstrated that diabetic patients had up to 50% reduction in AUC and a 40% reduction in C<sub>max</sub>. Pyrazinamide PK was reviewed in six studies and out of those, four observed lower PZA peak concentration and total plasma exposure in diabetic TB patients.

**Conclusions:** This is the first review to summarise the findings on the PK of TB drugs in DM patients. While there is high variability in findings and significant heterogeneity among studies, anti-TB drug concentrations were generally lower in DM patients. This implies DM may result in low drug exposures with potential adverse treatment outcomes.

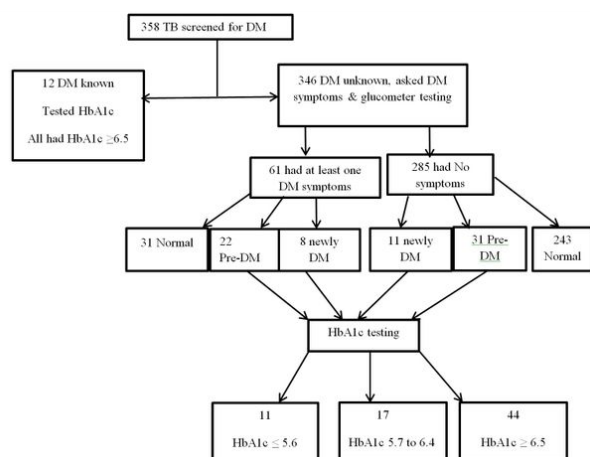
### OA-24-650-23 Optimizing diagnosis of diabetes mellitus among tuberculosis patients: preliminary findings from a multi-centre study in Tanzania

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**Background:** Evidence shows a 3-fold increase of active tuberculosis (TB) in populations with diabetes mellitus (DM) compared to those without DM. Therefore, a high suspicion for DM is needed in TB patients and vice versa. Also, dual TB/DM patients more frequent clinical manifestations for the two diseases which overlap and a high suspicious index for TB and DM is needed. Study was conducted to assess the implementation of a screening algorithm for the diagnosis DM in TB patients.

**Design/Methods:** The study was conducted in health facilities in Dar es Salaam, Iringa and Kilimanjaro regions, Tanzania. All diagnosed TB patients were screened for DM symptoms including polydipsia, polyphagia and polyuria, followed by randomly or fasting blood glucose testing to individuals with or without DM symptoms. All TB patients diagnosed with pre-DM or DM were further examined using glycated haemoglobin (HbA1c) to assess DM severity and HbA1c  $\geq 6.5\%$  or  $\geq 48\text{mmol/mol}$  was considered abnormal.

**Results:** From NOV 2019 through MAR 2020, 358 new TB patients were evaluated for DM, 62.6% were male; mean age  $\pm$  standard deviation (SD) of 41 years  $\pm$  17. Twelve (3.4%) TB patients had known for DM (Fig.1).



[Figure 1. Algorithm for DM screening in TB patients]

Sixty-one (17.6%) TB patients with unknown DM had at least one DM symptom. Thirty one (8.7%) of 358 recruited TB patients had DM, 19 (61.3%) of whom were newly diagnosed. HbA1c testing was evaluated in 72 TB patients (19 newly DM and 53 pre-DM), of which 11 (15.3%) had HbA1c  $\leq 5.6\%$ , 17 (23.6%) had  $\geq 5.7 < 6.5$  and 44 (61.1%) had  $\geq 6.5$ .

**Conclusions:** Screening measures for DM are highly recommended in patients with TB to improve diagnosis and early management of DM related complications.

### OA-24-651-23 Association of BMI, diabetes, and risk of tuberculosis: a population-based prospective cohort

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**Background:** China has dedicated significant public health resources to a strategy of active case finding of all individuals diagnosed with diabetes. However, it's unclear if all individuals with diabetes have increased risk of tuberculosis or there exists a high-risk groups of diabetes patients.

**Design/Methods:** We conducted a population-based census in eastern China including 27,809 individuals. We investigated risk factors for incident tuberculosis by excluding tuberculosis at baseline and linking all participants included in our study to the Tuberculosis Management Information System of Jiangsu Province. Follow-up for incident tuberculosis occurred over six years. We matched participants using unique health identity card numbers, name, age, birthdate, and address. To assess the association between body mass index (BMI), diabetes, and risk of tuberculosis, we constructed Cox Proportional hazard models adjusting for age, sex, smoking, alcohol use and Bacillus Calmette – Guerin scars in two steps,

(i) we compared the incident rate of tuberculosis in diabetes and non-diabetes without any stratification of BMI; (ii) we compared the incident rate of tuberculosis in diabetes and non-diabetes stratified by BMI. We divided BMI into two groups (BMI  $\leq 24$  and  $> 24$ ).

**Results:** Over six years, 95 individuals developed tuberculosis, an annual incidence rate of 52/100,000 (95% confidence interval [CI], 42.3–63.2). In multivariable Cox regression, participants with diabetes had 2.25 higher hazard (95% CI, 0.90–5.63,  $P=0.084$ ) compared with participants without diabetes. However, diabetes with BMI  $< 24$  (AHR=2.89, 95% CI: 1.15–7.29,  $P=0.025$ ) were risk factors for developing active tuberculosis. Participants considered overweight (BMI  $> 24$ ) and diagnosed with diabetes had similar risk as overweight participants without diabetes ( $P=0.985$ ).



**Conclusions:** In this population-based study of over 27,000 participants from China, individuals with diabetes had a higher risk of developing tuberculosis but only when they were not overweight, suggesting targeted screening should be considered.

### OA-24-652-23 Prevalence of diabetes mellitus among people tested for tuberculosis in urban Uganda

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**Background:** A rising prevalence of type 2 diabetes mellitus in countries where TB is endemic has led to an increased appreciation of diabetes as a population-level risk factor for TB. We sought to estimate the prevalence of diabetes among patients screened for TB in Uganda.  
**Design/Methods:** We enrolled people aged  $\geq 15$  years who were either tested for TB following symptomatic presentation to health facilities (August to December 2018 and July to December 2019) or screened for TB during symptom-neutral, community-wide active case finding (July to December 2019) within a community in Kampala, Uganda. Hemoglobin A1c (HbA1c) was measured using Eurolyser Cube (Eurolyser Diagnostica GmbH, Salzburg Austria). Diabetes was defined as HbA1c  $>48$  mmol/mol [DD3] ( $>6.5\%$ ) and prediabetes as 42–48 mmol/mol (6.0–6.5%).  
**Results:** Of 463 participants, 381 (82%) had HbA1c results; of participants with HbA1c results, 132 (35%) were diagnosed with TB. Among all participants with HbA1c results, the prevalence of diabetes was 2.9% (95% confidence interval (CI) 1.5–5.1%) and of prediabetes was 5.0% (95% CI 3.0–7.7%). Diabetes prevalence was similar among people with TB (2.3%, 95% CI 0.5–6.5%) compared to TB-negative individuals (3.2%, 95% CI 1.4–6.2%). The prevalence of diabetes was also similar among people seeking care at health facilities compared to those tested in the community, although all of the people found to have both diabetes and TB were symptomatic patients evaluated at health facilities (Table 1).  
**Conclusions:** The prevalence of diabetes among people tested for TB in urban Uganda was low and not associated with TB status among either patients presenting at health facilities or participants in community-based TB screening. Further evaluation of TB treatment outcomes

among people with diabetes and pre-diabetes may help determine the importance of monitoring diabetes in this population.

Characteristics	Health Facility evaluation, TB positive (n=86)	Health Facility evaluation, TB negative (n=161)	Community screening, TB positive (n=46)	Community screening, TB negative (n= 88)
Female	34 (40%)	91 (57%)	17 (37%)	53 (60%)
Male	52 (60%)	70 (43%)	29 (63%)	35 (40%)
Age in years, median (IQR)	32 (26-42)	33.5 (25-43)	28 (24-35)	26 (21-35)
Hba1c, in mmol/mol, median (IQR)	30 (25-36)	31 (26-36)	31 (25-36)	30 (25-36)
Diabetes	3 (3.5%)	6 (3.7%)	0 (0%)	2 (2.3%)
Prediabetes	6 (7.0%)	5 (3.1%)	2 (4.4%)	6 (6.8%)

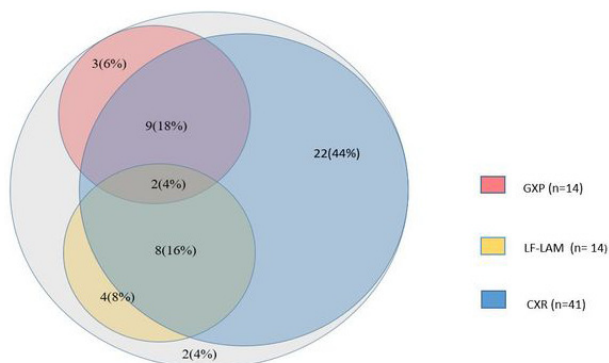
[Table 1: Characteristics of people with TB (symptomatic and asymptomatic) compared to TB-negative controls identified from health facilities and the community in Kampala, Uganda.]

### OA-24-653-23 Screening hospitalized patients with diabetes mellitus for tuberculosis in rural South Africa

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**Background:** The risk of tuberculosis (TB) and adverse TB treatment outcomes in patients with diabetes mellitus (DM) are higher than the general population. Active case finding and early treatment could address this, especially in settings with dual burden of disease such as South Africa.  
 This study aims to describe the yield of systematic TB screening among hospitalized DM patients in rural KwaZulu-Natal, South Africa.  
**Design/Methods:** From March 2019 to March 2020, we systematically assessed patients aged  $\geq 18$  years admitted to two hospitals for DM and TB. For patients known or diagnosed with DM, we did TB symptom screening and chest X-ray (CXR). We performed GeneXpert MTB/RIF Ultra for patients who were able to produce sputum and urine LF-LAM for HIV-positive patients.  
**Results:** Out of 4015 patients assessed during the study period, we identified 718 with DM. Among these, 12 were on TB treatment at admission. We screened 706 patients with a median age of 64 years (interquartile range (IQR) 55-73) and 75.2% (531) were females. Among 692

patients with known HIV status, 16.5% (114) were HIV-positive. Among 630 patients with HbA1c recorded, 44.0% (277), 35.4% (223) and 20.6% (130) had HbA1c >10%, 7.1-10% and ≤7% respectively.



[Figure 1. Venn diagram showing the methods of tuberculosis diagnosis\* and the incremental yield of GeneXpert (GXP), urine lateral flow lipoarabinomannan (LF-LAM) and chest X-ray (CXR) in hospitalized diabetic mellitus patients

\*Two patients were diagnosed clinically]

The proportion of patients diagnosed with TB was 7.1% (50). The yield was higher in HIV-positive than HIV-negative patients (17.5% (20/114) vs. 5% (29/578),  $p < 0.001$ .) Three out of 268 patients with initial negative symptom screening were diagnosed. CXR, GeneXpert, and LFB-LAM were the main methods of diagnosis and their diagnostic yield is depicted in figure 1. Majority of the patients (94.0% (47)) had pulmonary TB. All patients who had bacteriological confirmation had rifampin-sensitive TB.

**Conclusions:** Systematic screening and diagnosis of hospitalized diabetic patients for TB showed a very high yield. This should be part of routine hospital care in settings with high, dual TB and DM.

## OA-24-654-23 Performance of random plasma glucose compared to glycated hemoglobin in screening for diabetes in Filipino persons with TB

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**Background:** Diabetes mellitus (DM) is a common comorbidity in persons with tuberculosis (TB). In the Philippines, however, many diabetes cases are undiagnosed, and glycated hemoglobin (HbA1c) is not widely used as diabetic diagnostic test. We assessed the performance and costs of random plasma glucose (RPG) alone and a two-step RPG/HbA1c  $\geq 6.5\%$  to screen for diabetes compared to (HbA1c%) alone in persons with newly diagnosed TB.

**Design/Methods:** This analysis uses baseline data from non-pregnant adult participants enrolled into the ST-ATT cohort (ISRCTN16347615) from 15 public facilities in 3 regions of Philippines between 2018-2020, within 5 days of starting TB treatment. Diabetes (defined as HbA1c  $\geq 6.5\%$ ) was compared with RPG  $\geq 200\text{mg/dL}$  using finger-prick capillary blood samples. Sensitivity and specificity of RPG and the two-step RPG/HbA1c  $\geq 6.5\%$  was compared to HbA1c  $\geq 6.5\%$  as gold standard. Individuals with previous diagnosis of DM, or taking DM medications were excluded from analyses. Costs of RPG and HbA1c tests were obtained from local government hospitals at 100-200PHP and 400-500PHP respectively.

**Results:** 684 individuals were eligible for analysis. Of 100 persons with HbA1c  $\geq 6.5\%$ , 38 had RPG  $\geq 200\text{mg/dL}$ , and the sensitivity and specificity of RPG  $\geq 200\text{mg/dL}$  were 38% and 100%. If RPG  $\geq 110\text{mg/dL}$  was used, sensitivity and specificity were 75% and 60%. If a 2-step process of initial screening using RPG  $\geq 110\text{mg/dL}$  followed by HbA1c, the number of HbA1c tests would have been reduced to 271, but would have missed 25/100 persons with diabetes at a cost-saving of 27%. Similarly, screening with RPG  $\geq 100\text{mg/dL}$  followed by HbA1c, 17/100 persons with diabetes would have been missed with a minimal cost-saving of 6%.

**Conclusions:** RPG only and the two-step RPG/HbA1c were not efficient to screen for diabetes in this setting. TB induced hyperglycemia may contribute to incorrect diabetes classification and will be investigated in repeated data collected during the cohort.

## OA-25 TB: deep into molecular structure

### OA-25-655-23 Transmission of *Mycobacterium tuberculosis* genotypes and their association with drug-resistance in Mumbai, India

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**Background:** Transmission of drug resistant (DR) *Mycobacterium tuberculosis* complex (Mtb) strains of particular subtypes/genotypes in high burden areas like Mumbai poses a scenario of rapid spread of DR Mtb strains. We attempt to determine transmission levels through genome-based cluster analysis of Mtb strains from Mumbai city using whole genome sequencing (WGS) considering very few studies in such high incidence settings.

**Design/Methods:** WGS was performed for a total of 1897 clinical Mtb isolates from TB patients that were collected from a tertiary care centre in Mumbai, India between February 2017- May 2018. Basic WGS data analysis was done with MTBseq (v1.0.3) and Ridom SeqSphere+ was used for clusters analysis based on a core genome Multi-Locus Sequence Typing (cgMLST) approach with a maximum threshold of 12 allelic differences between two strains.

**Results:** Of 1897 samples analysed, cgMLST analysis identified 815/1897 (43%) patients belonged to 101 clusters with cluster size ranging from 2-260 isolates. Strains of the Beijing/East Asia lineage represented approximately 40% (n=764) of all strains investigated (predominantly Asian/African2 sub-lineage, 47.3%), while the remaining 60% constituted of strains of other lineages e.g. Delhi/CAS. Univariate analysis revealed that the strains belonging to the Beijing genotype were more frequently associated with drug resistance as compared to drug susceptibility (OR 29.959; 95%CI; 20.8-43.0; p<0.0001); similarly clustering was more frequent in Beijing genotype as compared to non-Beijing strains (OR 31.764; 95%CI; 24.6-41.0; p<0.0001). Detailed SNP-based cluster analysis of first three prominent allele clusters of Beijing genotype (n=475) showed that 50% (n=236) of isolates had high transmission rates, even using a strict threshold of 5 SNPs distance. Strains were prominently associated with pre-extensively drug resistance (n=298, 62.6%)/extensively drug resistance (n=122, 25.8%). Detailed analyses are ongoing.

**Conclusions:** Our study provides evidence of probable transmission of DR Mtb strains of the Beijing genotype in Mumbai (38.4%). Genomic epidemiology is essential to better define transmission networks.

### OA-25-656-23 Delineate tuberculosis transmissions for outbreak investigations using whole genome sequencing in Taiwan

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**Background:** Tuberculosis (TB) is a major notifiable disease in Taiwan. For facilitating TB control, we used whole-genome sequencing (WGS) to delineate transmission networks and to investigate the benefits of WGS.

**Design/Methods:** We included cases of 2 TB clusters linked by space oligonucleotide typing and mycobacterial interspersed repetitive unit variable tandem repeat typing in the national clusters C9 and C36, identified during 2009-2018 and 2012-2018, respectively. The whole genome of *Mycobacterium tuberculosis* was sequenced using the Illumina MiSeq or HiSeq platform. To confirm an outbreak, the transmission events between cases within clusters were calculated using thresholds of  $\leq 5$  (definite) and  $\leq 15$  (probable) single nucleotide polymorphisms (SNPs) difference between isolates. A structured questionnaire was used to collect social network information. A cluster was defined as isolates with identical genotypes, and an outbreak was defined as clustered cases with epidemiological links (epi-links).

**Results:** The TB cluster (C36) consisting of 28 cases had total 21 SNPs difference and  $\leq 5$  SNPs between their isolates. C36 was clearly identified as an outbreak originated from a junior high school in 2012. However, 5 cases having no known epi-links were excluded.

We further analyzed a MDR-TB cluster (C9) consisting of 17 cases including 16 cases from same county and their isolates had  $\leq 14$  SNPs difference. The remaining case from neighboring county whose isolate having 68 SNPs and 5 cases without epi-links were excluded. We confirmed C9 as an MDR-TB outbreak with 11 cases from the same aboriginal village. Of note, even though WGS could effectively assist TB contact tracing, we still observed missing epi-links in some cases in the same cluster. Preliminary results showed that higher SNP threshold might be required to define a MDR-TB outbreak.

**Conclusions:** WGS still needs to be combined with classical epidemiological methods for improving outbreak investigations. Importantly, different SNP thresholds have to be applied to define outbreaks.

### OA-25-657-23 Characterization of mutations in the Rifampicin resistance determining region of the *rpoB* gene associated with Multi Drug Resistant tuberculosis in Zambia

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**Background:** Xpert MTB/RIF assay is the first line diagnostic tool for initial detection of Drug Resistant (DR) TB in Zambia but does not detect INH resistance. Furthermore, access to full Drug Susceptibility Testing (DST) is limited. Characterization of *rpoB* gene mutations and understanding of how these mutations associate with INH resistance can provide insight on how laboratories can further interpret Xpert results to aid initial management of DR TB in the absence of DST results.

**Design/Methods:** We retrospectively reviewed results of MTBRDplus Line Probe Assay (LPA) tests performed at the National TB Reference Laboratory (NTRL) in 2019. The observed *rpoB* mutations were characterized and correlated with corresponding INH resistance. The relationship between regions of the *rpoB* gene and Xpert probes was also examined.

**Results:** Results for 49 isolates with mutations in the *rpoB* gene were included in the analysis. Of these, 37 (76%) isolates were MDR while 12 (24%) were Rifampicin mono resistant. Mutations were most commonly found in the 523-529 (37%) and 529-533 (35%) regions of the *rpoB* gene. All isolates with mutations in the *rpoB* regions 523-529 (16) and 529-533 (13) showed high level resistance to IHN. Three isolates that showed mutations in the region 507-511 showed low level INH resistance. Five isolates showed mutations in multiple regions and of these, 2 showed high level INH resistance while 3 showed low level INH resistance.

The *rpoB* regions 523-529 and 529-533 correspond to Gene Xpert probes D and E respectively while the *rpoB* region 507-511 corresponds to Gene Xpert probe A.

**Conclusions:** These results suggest that in our setting, Xpert RR results involving a missing probe D or E can be associated with high level INH resistance while those involving a missing probe A can be associated with low level INH resistance. Further investigations involving larger sample sizes are needed to validate this suggestion.

### OA-25-658-23 MIRU-VNTR genotyping indicates marked heterogeneity of tuberculosis transmission in the United States, 2009-2018

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**Background:** The validity of models to estimate the impact of tuberculosis (TB) control strategies relies on input parameters such as the number of secondary cases produced by an individual source case, the effective reproductive number,  $R$ . There might be substantial individual heterogeneity in  $R$ ; failing to account for this could introduce bias. We estimate  $R$  using genotyping and surveillance data from the Centers for Disease Control and Prevention (CDC) and calculate the dispersion parameter of this distribution,  $k$ , a measure of transmission heterogeneity.

**Design/Methods:** We model transmission as a subcritical branching process using a negative binomial distribution to estimate  $R$  and  $k$ . We use spoligotype and 24-locus MIRU-VNTR genotyping data from the National Tuberculosis Genotyping Service (NTGS) and surveillance data from the National Tuberculosis Surveillance System (NTSS). We defined cases as being in the same cluster if they were reported in the same county within a two-year period and their genotypes matched. Cases among persons with recent U.S. arrival (<6 months) were assumed to have contracted TB abroad and were considered as source cases but not secondary cases. For sensitivity analysis, we excluded extrapulmonary TB cases.

**Results:** During 2009–2018, 85,958 TB cases were reported to NTSS. Complete MIRU-VNTR data were available for 55,330 cases, yielding an estimate of  $R=0.59$  and  $k=0.05$ ; the low value of  $k$  indicates a small number of source cases produce a disproportionate number of secondary cases. Results were similar when extrapulmonary TB cases were excluded.

**Conclusions:** TB cluster size has a highly skewed distribution, consistent with the conclusion that a small number of cases accounts for a large proportion of TB transmission in the United States. Similar findings have been reported for the Netherlands, a comparable low-burden setting. Studies describing TB transmission or modelling the impact of control strategies should account for heterogeneity in  $R$ .

**OA-25-659-23 Tuberculosis Molecular Bacterial Load Assay (TB-MBLA): a method to speed early phase tuberculosis TB clinical trials**

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**Background:** Tuberculosis (TB) drug development is slow and expensive. Pharmacodynamic (PD) biomarkers in Phase II studies measure drug efficacy to define phase III studies would be appropriate. Current culture-based techniques impose significant delay and cannot be used for treatment monitoring. TB-MBLA is a molecular measure of the number of live bacteria by detecting 16S rRNA, allowing rapid treatment monitoring.

**Design/Methods:** Serial sputum samples from the 5-week high dose rifampicin II (HIGHRIIF2) Phase 2B clinical trial were used. RNA was extracted and used to estimate bacterial load by TB-MBLA. TB-MBLA results were compared with Serial Sputum Colony Count (SSCC) and Mycobacteria Growth Indicator Tube (MGIT).

**Results:** Of 150 patients enrolled in the HR2 trial, 24 were selected for this study. We demonstrated that while contamination resulted in a high percent (30.4 %) of missing data points in culture, TB-MBLA produced a complete data set. TB-MBLA-measured bacterial load correlated with solid culture SSCC (p=0.0001) and MGIT time-to-positivity (p=0.011). On average, TB-MBLA measured 2 log<sub>10</sub> CFU/ml higher bacterial load than colony counts on solid agar over the 5-week treatment period. Compared to the standard 600 mg dose, higher doses of rifampicin (900 mg and 1200 mg) did not significantly improve early bactericidal effect (p=0.95 and 0.51, respectively).

**Conclusions:** TB-MBLA can detect changes in viable bacillary count rapidly and could replace culture. Importantly, results are obtained within 24 hours and are not compromised by sample contamination. It is robust, reproducible and sensitive; qualities critical for simplifying clinical trials and routine clinical practice.

**OA-25-660-23 Impact of randomized blinded rechecking program on the performance of the acid-fast bacilli microscopy laboratory network in Uganda: an eleven years' retrospective study**

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**Background:** Microscopy has remained the initial test for most presumptive tuberculosis (TB) patients and only susceptible TB treatment monitoring tool in Uganda. Uganda began a Randomized Blinded Rechecking (RBRC), an External Quality Assurance program in 2008. We set out to evaluate the impact of this program on the performance of Uganda's Microscopy Laboratory Network.

**Design/Methods:** A retrospective study was conducted from 2008 to 2018 across all laboratories in Uganda. Frequencies of test results were calculated in Microsoft Excel 2013 and then presented in tables. A contingency table was used to obtain sensitivity and specificity. Using STATA 15A, we did a chi-squared trend test to evaluate whether there was a linear trend between years of analysis and test results considered. A p-value of less than 0.05 was considered statistically significant at a 95% confidence level.

**Results:** Of the 311,859 smears re-checked over eleven years, False-Positive and High False-Positive errors decreased from 12.8% to 7.5% and 10% to 5.8% respectively. False Negative, High False-Negative and Quantification errors decreased from 2.9% to 0.5%, 2.1% to 0.4% and 6.0% to 1.2% respectively from 2008 to 2018.

Test result	Year of analysis											P-Value
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	
False-Positive Errors (%)	12.8	10.0	9.8	7.9	8.8	8.9	8.3	7.6	8.5	7.6	7.5	<0.0001
High False-Positive Errors (%)	10.0	8.0	7.8	5.7	6.8	7.0	7.0	6.5	7.2	6.3	5.8	<0.0001
False-Negative Errors (%)	2.9	2.5	2.6	1.8	1.7	1.2	1.0	0.8	0.8	0.7	0.5	<0.0001
High False-Negative Errors (%)	2.1	1.9	1.9	1.3	1.3	1.0	0.8	0.6	0.7	0.5	0.4	<0.0001
Quantitative Error Errors (%)	6.0	3.7	3.1	2.4	1.8	1.6	1.6	1.6	1.3	1.8	1.2	<0.0001

[Table]

The p values for the Chi-squared test for reducing trends of all errors were below 0.05. Laboratories with more than one High-False Positive and one False-Negative er-

ror decreased from 12% to 4% and 12% to 3% respectively from 2008 to 2018. Laboratories with 100% True Positives rose from 57% in 2008 to 74% in 2018. Sensitivity and specificity, when compared to the re-checking controller, increased from 93% to 97% and 97% to 100% respectively from 2008 to 2018.

**Conclusions:** The study reveals a statistically significant linear reduction of errors upon the continuous implementation of the RBRC program and also an improved sensitivity and specificity of AFB microscopy. We recommend introduction and continuous implementation of RBRC in countries still performing AFB microscopy.

## OA-26 Using digital technology for TB elimination

### OA-26-661-23 The use of GIS technology and self-reported data to characterize congregate settings with high potential risk for tuberculosis transmission in an urban African area

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**Background:** It has been suggested that in high-burden areas, tuberculosis transmission happens in indoor congregate settings. The use of GIS technology coupled with data provided by infectious TB cases can inform local public health interventions that target these congregate settings with high potential risk for tuberculosis transmission.

**Design/Methods:** This is a retrospective cohort study conducted in an urban area in Uganda from August 2019 to February 2020 among recently diagnosed tuberculosis cases. Participants enrolled in public clinics provided us with a list of the number and characteristics of the community locations, apart from their homes, that they visited in the three months before diagnosis, and we collected their geographical coordinates. We characterized the locations as high-risk congregate settings if the participants reported more than ten persons in the location when it was visited and if it was an indoor environment. We created a heatmap of the study area, showing the location of these congregate settings.

**Results:** Enrolled cases (n=41) were primarily men (63%) and young adults (median age: 34 years). Participants listed a median of 8 locations (range: 2-30) for a

total of 486 locations. We obtained coordinates for 95% of these locations. High-risk congregate settings accounted for 56 (12%) of them. High-risk settings were primarily worship centers (41%), entertainment venues (23%), workplace of the case (14%), and healthcare settings (11%).

Most participants reported visiting these locations after the onset of cough (92%), and these locations were visited a median of 3 days (IQR 1-5) in the 30 days before the TB diagnosis. High-risk congregate settings concentrated in an area of approx. 3 km<sup>2</sup> of the study area (Figure).



[Figure. Heatmap, urban area Uganda.]

**Conclusions:** Self-reported locations by tuberculosis patients indicated geographic heterogeneity of transmission. Aggregated self-reported locations may help guide public health officials into identifying potential high transmission zones in urban settings.

### OA-26-662-23 Bundling innovations for public private mix: experience of artificial intelligence augmented chest X-Ray screening and truelab for diagnosis

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**Background and challenges to implementation:** In India, Nagpur is among the top 20 cities with the highest tuberculosis (TB) incidence. With more than 50 percent of the patients seeking care from the private sector, informal providers (IFP) are usually the first point of contact.

As part of a TB REACH project, PATH implemented a Public Private Mix (PPM) initiative by networking with 316 informal providers and equipped them with two new technologies:

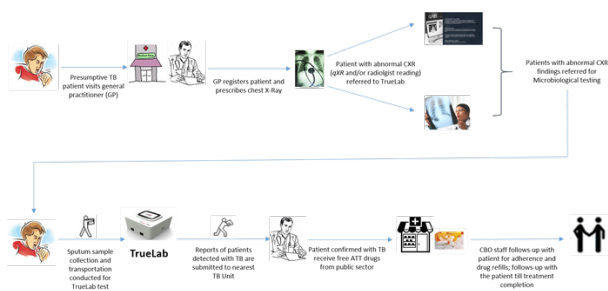
1) *qXR*—an artificial intelligence (AI) based screening tool for screening; and,



2) TrueLab – a chip based Nucleic Acid Amplification test (NAAT) test for confirmation of TB through portable battery-operated PCR machine.

Case notifications were done in public sector.

**Intervention or response:** All presumptive TB patients seeking care at the engaged IFPs were offered free CXR vouchers and were screened by the radiologists in private CXR facilities and *qXR* technology. The technology reads each CXR for eight abnormalities. All screened TB-positives through the radiology report and Qure.ai were sent for microbiological testing using TrueLab, which was placed in a public-sector hospital. Patients with confirmed TB through TrueLab were notified in the public sector. The patients were linked for treatment initiation in public facilities and followed up for treatment adherence and outcomes.



[Figure.]

**Results/Impact:** From January 2019 to February 2020, 8,731 presumptive TB patients were screened with CXR, 2,303 reported abnormal findings and 224 patients were detected with pulmonary TB. Of those, 184 (82 percent) were microbiologically confirmed. There was a 40 percent increase in overall pulmonary TB case notifications and in bacteriological case detection in the fourth quarter of 2019 compared to 2018 in public sector.

**Conclusions:** Our intervention demonstrates that by using newer technology innovations and setting up informal provider referral system for public sector, it is possible to reach the missing million cases and make significant strides toward ending TB in India.

## OA-26-663-23 Reducing TAT (Turn-Around-Time) by transitioning from paper based to DSC (Digital Signature Certificates) based approval of Direct Benefit Transfers under NTEP (National Tuberculosis Elimination Program), India

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**Background and challenges to implementation:** Various Direct Benefit Transfer schemes have been introduced by the Govt of India to reduce catastrophic costs to patients. These benefits are provided to respective beneficiaries after due process of verification and approval. These are done Digitally through an interface between two systems; Nikshay, the National TB patient management and Surveillance System for Tuberculosis and the Public Financial Management System (PFMS). One calculates and processes benefits based on eligibility of various beneficiaries while the other manages the finance, accounting and payments. For payment of each benefit, three level of approvals are required; the first two approvals are in Nikshay and the third was traditionally a paper based approval of a digital payment advice done through Public Financial Management System (PFMS). This paper based approval results in delay of communication between signatories and then submission to the bank.

**Intervention or response:** A Digital Signature Certificate (DSC) based approval from the authorized signatories effectively removes the delay between approval and submission of payment advice to bank. This was expected to improve transparency and security of payments through the digital end-to-end process and improve the timeliness and efficiency of digital payments.

**Results/Impact:** The turn-around-time (TAT) was defined as time between Payment approval to actual payment to beneficiary in days. Before implementation of the DSCs the average TAT varied between 12 to 15 days; while after implementation, this reduced to an average of approximately 7 days. This system also permitted processing of approximately two times higher volumes of payment.



**Conclusions:** Adopting a end-to-end processing on an electronic/ digital platform has significant returns in terms of process efficiency and transparency. It appears to achieve near-real time communication of process status to all stakeholders resulting in better accountability. Such systems for processing all types of transactions need to be encouraged.

### OA-26-664-23 Improving tuberculosis patients' treatment adherence via electronic monitors and an app versus usual care in Tibet: a pragmatic randomised controlled trial

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**Background:** Poor treatment adherence is a serious challenge to effective tuberculosis (TB) control in Tibet. This study aims to evaluate the effectiveness of using new technologies, including electronic monitors (e-monitors) and a smartphone app, to improve treatment adherence among new pulmonary TB patients in Tibet, China.

**Design/Methods:** This is a prospective, pragmatic, multicentre, individual-randomized controlled trial with blinded outcome evaluation, and unblinded treatment. New pulmonary TB patients of three counties/districts in Shigatse, Tibet have been randomized to either the intervention or control arm in a 1:1 ratio at the time of their diagnoses since December 2018. All patients in both arms were treated according to the WHO standard TB treatment regimens and China National TB program guidelines, and received their medicines in e-monitors which could report their medication adherence history to the server every day.

Additionally, in the intervention arm, e-monitors remind patients of taking medicines with recorded human voice and share the medication adherence history with health staff via a smartphone app so that video observed treatment could be provided when adherence was problematic. Medication adherence data were collected through the server for interim analysis.

**Results:** We here report the trial progress by the end of March 2020. We have recruited 123 eligible patients, of which 73 were allocated in the intervention arm and 50 in the control arm, with 46/27 patients (intervention/control) still on treatment. Total planned doses were 10,203 in the intervention arm and 7,295 in the control arm.

Medication adherence rate was significantly higher in intervention arm (98.9%) than in control arm (40.0%) with p value less than 0.05. We report the responses of applying the e-application for TB patients during the COVID outbreaks.

**Conclusions:** Interim analysis results implied that electronic monitor and its app function improves medication adherence among TB patients and becomes more accepted during the COVID outbreaks.

### OA-26-665-23 Preliminary results of a randomized trial comparing traditional in-person directly observed therapy (DOT) and video-based DOT for monitoring tuberculosis treatment

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**Background:** We conducted a randomized two-period cross-over trial in New York City Health Department (NYCDOH) Tuberculosis Clinics to evaluate whether directly observed therapy (DOT) conducted using "smart" electronic devices (eDOT) can attain a level of treatment adherence at least as favorable as traditional in-person DOT (ipDOT).

**Design/Methods:** We randomized TB patients to ipDOT or eDOT. Patients aimed to complete 20 medication doses with one DOT method, then switched methods for another 20 doses. Care was provided per NYCDOH policy.

Our primary outcome was the difference in the percentage of medication doses that were completed when observed by eDOT vs ipDOT. All doses scheduled for DOT on non-holiday weekdays were included; doses were excluded if the treating clinician withheld medications, or if the patient was admitted to a facility for inpatient care. We conducted an intention-to-treat analysis. The percentage of doses completed was estimated as a least-square mean from mixed effects logistic regression models, accounting for within-subject correlation. Analysis was restricted to patients with  $\geq 10$  doses observed with each DOT method. The non-inferiority margin was  $\leq 10\%$  for the percentage-difference between DOT methods.

**Results:** Between July 2017 and October 2019, 216 (26%) of 820 eligible patients were enrolled, and 174 (81%) met criteria for statistical analysis. Their median age was 40 years [range:17-86], 66% were male, 37% were Asian/Pacific Islander, and 31% were Hispanic.

Among 6,801 doses, the intention-to-treat model estimated the percentage of doses completed was 90.0% [88.0, 91.7] when observed by eDOT versus 88.0% [85.9, 89.8] by ipDOT. The percentage-difference between the DOT methods was +1.9% [+0.5, +3.3]. Per-protocol and empirical ("as treated") analyses yielded similar results.

**Conclusions:** Our results support a conclusion that eDOT is non-inferior to ipDOT in this large urban TB program with a long history of successful implementation of ipDOT.

**OA-26-666-23 Assessing Adverse Events Among Patients Using In-person and Electronic Directly Observed Therapy (DOT)**

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**Background:** We conducted a randomized crossover trial comparing traditional in-person directly observed therapy (ipDOT) with electronic directly observed therapy (eDOT) for tuberculosis (TB) treatment in New York City TB clinics. We assessed frequency and severity of adverse events (AE) and time to access care by DOT method.

**Design/Methods:** Participants reported medication side effects and health-related issues at the beginning of DOT sessions and monthly clinic visits. Providers graded symptom severity using the National Cancer Institute Common terminology criteria. Data were analyzed by DOT method immediately prior to reporting AEs. Reported symptoms were not mutually exclusive.

**Results:** Of 216 enrolled participants, 63 (29.2%) experienced 87 AEs. (See Table)

		Cumulative AEs N=87	eDOT AEs N=47	ipDOT AEs N=40
Most Commonly Reported Symptoms	Nausea or Vomiting or Stomach Pain	42 (48.3%)	21 (44.7%)	21 (52.5%)
	Rash or Skin Problems	21 (24.1%)	11 (23.4%)	10 (25.0%)
	Malaise or Fatigue	17 (19.5%)	7 (14.9%)	10 (25.0%)
	Severe AEs (Graded according to National Cancer Institute Common terminology criteria for adverse events)	11 (12.6%)	7 (14.9%)	4 (10.0%)
Severity of Adverse Events (AEs)	Side effects were NOT consistent with the pharmaceutical package insert for prescribed TB medications	4 (4.6%)	3 (6.4%)	1 (2.5%)
	Patient was Hospitalized	9 (10.3%)	6 (12.8%)	3 (7.5%)
	Life-threatening; urgent intervention indicated	1 (1.1%)	1 (2.1%)	0 (0.0%)
Adverse Event Management	Time in days, after signs and symptoms began until the patient discussed the problem with a healthcare provider	1.0 [0.0:2.5]	1.0 [0.5:3.0]	1.0 [0.0:2.0]

eDOT AEs = Adverse event occurred when participant was using live or recorded video DOT or had used eDOT immediately prior to the event  
 ipDOT AEs = Adverse event occurred when participant was using clinic- or field-based DOT or had used ipDOT immediately prior to the event  
 All continuous variables are expressed by median [Quartile 1; Quartile 3]  
 All category variables are expressed by frequency (column percentage)

[Table: Symptoms, Severity, and Management of Adverse Events by DOT Method]

Of 87 AEs, the most commonly reported symptoms included: nausea, vomiting or stomach pain 48.3% (n=42), rash or skin problems 24.1% (n=21), and malaise or fatigue 19.5% (n=17).

Most AEs 87.4% (n=76) were graded as mild or moderate; 14.9% (n=11) were graded as severe. Of 11 severe AEs, 4 were not consistent with TB medication pharmaceutical package inserts, 9 required hospitalization, and one was considered life-threatening.

54.0% (n=47) of AEs were reported by participants using eDOT, compared to 46.0% (n=40) reported by participants using ipDOT.

Time between symptom onset and patients' discussions with providers was similar by DOT method (median 1 day [Q1: 0; Q3: 2.5]). When using eDOT, most patients initially discussed AEs with providers during non-routine clinic visits (43.5%, n=20), via program-initiated phone calls (26.1%, n=12), and routine clinic visits (17.4%, n=8). When using ipDOT, most patients initially discussed AEs with providers during non-routine clinic visits (55.0%, n=22), routine clinic visits (22.5%, n=9), and patient-initiated phone calls (15%, n=6). No patients were switched from eDOT to ipDOT due to AEs.

**Conclusions:** AE types and severity, affecting almost one-third of patients, were similar across DOT methods, with comparable time to medical attention.

**OA-27 The social impact of TB in Europe**

**OA-27-667-23 Social risk factors for TB in England: A National Point Prevalence Study 2019**

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**Background:** Current TB surveillance data in the UK only collects data on four social risk factors (SRF), alcohol and drug misuse, homelessness and imprisonment (SRFs) underestimating the true proportion of cases with social and economic problems. To better understand the breadth of social inequalities experienced by people with TB, a national point prevalence study was undertaken for all patients in treatment for active TB in England during a week in June 2019.

**Design/Methods:** Local TB services completed an online questionnaire for each patient in their care. These data were matched to Enhanced TB surveillance (ETS) data for analysis with initial associations between SRFs and other social needs explored through cross-tabulation and chi-squared tests.

**Results:** Completed questionnaires were received from 1596 of the 2200 people estimated to be in care during the study week, a response rate of 72%.

In this study, 15% of people diagnosed with TB had at least one of the four SRF above, higher than that reported in national surveillance to date. A total of 25% of TB cases in this cohort had a wider range of social problems, being from vulnerable migrant groups, prisoners, those who misuse drugs and alcohol, or experiencing mental health issues or homelessness – defined as underserved populations (USPs).

**Background and challenges to implementation:** Current TB surveillance data in the UK only collects data on four social risk factors (SRF), alcohol and drug misuse, homelessness and imprisonment (SRFs) underestimating the true proportion of cases with social and economic problems. To better understand the breadth of social inequalities experienced by people with TB, a national point prevalence study was undertaken for all patients in treatment for active TB in England during a week in June 2019.

**Intervention or response:** Local TB services completed an online questionnaire for each patient in their care. These data were matched to Enhanced TB surveillance (ETS) data for analysis with initial associations between SRFs and other social needs explored through cross-tabulation and chi-squared tests.

**Results/Impact:** Completed questionnaires were received from 1596 of the 2200 people estimated to be in care during the study week, a response rate of 72%.

In this study, 15% of people diagnosed with TB had at least one of the four SRF above, higher than that reported in national surveillance to date. A total of 25% of TB cases in this cohort had a wider range of social problems, being from vulnerable migrant groups, prisoners, those who misuse drugs and alcohol, or experiencing mental health issues or homelessness – defined as underserved populations (USPs).

**Conclusions:** The identification of additional social factors not currently recorded in national surveillance should inform future National TB Policy to help meet the wide range of social need experienced by people with TB.

## OA-27-668-23 Country-specific approaches and effectiveness of latent tuberculosis screening targeting migrants to Europe

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**Background:** Estimates suggest a reservoir of 1.3 billion cases of latent tuberculosis infection (LTBI) globally. In migrants in low-incidence countries in Europe most cases of active TB are thought to arise from reactivation of LTBI. There is an urgent need to better understand how countries approach LTBI screening in recently arrived migrants.

**Design/Methods:** We did a systematic review and meta-analysis to explore treatment uptake and adherence among LTBI positive migrants globally. The protocol was PROSPERO registered (CRD42019140338) and follows PRISMA guidelines. We did a semi-structured survey of TB experts in 32 EU/EEA countries and Switzerland exploring policy and practice around LTBI screening approaches targeting migrants.

**Results:** 37 studies were included in the review, including data on 30,645 LTBI-positive migrants. 51% (95% CI = 38-64%; I2 = 99.21%) testing positive go on to initiate and complete treatment. 74% (95% CI = 0.66-0.91; I2 = 99.19%) who initiate treatment ultimately completed it. A variety of patient and provider-linked factors account for migrants not initiating and completing treatment.

13 (40%) of 32 EU/EEA countries reported targeting migrants for LTBI screening, focusing on migrants from high-burden countries, though definitions varied. Most countries follow similar diagnostic approaches for LTBI, with 7 (53%) of countries using use RIF+INH/3 months as their first choice treatment. Experts reported that migrants were a group with higher drop-out rates, reporting a need for greater awareness about LTBI within migrant populations.

**Conclusions:** Improvements in the LTBI care cascade are needed for migrant patients, particularly with respect to the initiation of treatment amongst those testing positive. Greater focus must be given to designing and delivering effective LTBI programmes to migrants if we are to improve health and support global TB eradication.

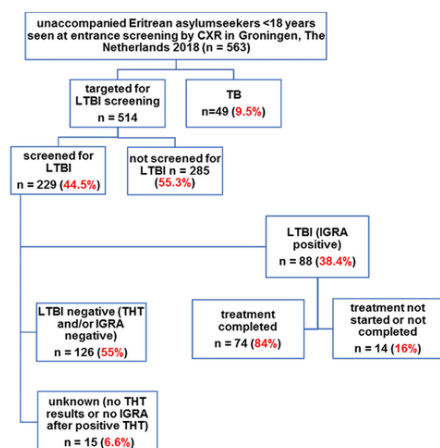
**OA-27-669-23 High TB and latent TB infection prevalence among minor Eritrean asylum seekers in the Netherlands; importance of travel history**

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**Background and challenges to implementation:** In 2018/19, after radiographic screening at the Dutch national reception centre in 2018, tuberculosis (TB) was diagnosed in 49 of 563 unaccompanied minor asylum seekers (UMAs) from Eritrea (TB prevalence rate 8 526 per 100 000). Most of them did spent many months in overcrowded conditions in Libya. Screening for latent TB infection (LTBI) is not routine in the Netherlands. Because intense TB transmission in Libya was suspected, attempts were made to examine all other 514 UMAs for LTBI, to prevent progression to active TB in more children.

**Intervention or response:** Locating Eritrean UMAs in decentralised residential asylum seeker centres and offer screening with a tuberculin skin test (TST), followed by interferon gamma release assay (IGRA) when positive (TST ≥ 5mm).

**Results/Impact:** Of 514 targeted UMAs 229 could be tested while 285 could not be found or did not report for screening for different reasons. Among those tested 88 (38.4%) were diagnosed with LTBI (LTBI prevalence rate 3 870 TB cases per 100 000 children), 126 tested negative (55%) and in 15 (6,5%) results were unknown or inconclusive. Of those diagnosed with LTBI 74 (84%) started and completed preventive treatment (Figure 1).



[Figure 1]

**Conclusions:** In 2018/19 in the Netherlands a high TB and LTBI prevalence rate among minor Eritrean asylum seekers was found, probably related to prolonged incarceration in Libya. Comprehensive LTBI screening was hindered by logistical difficulties in tracking down UMAs targeted, for various reasons. After a recent evaluation of radiographic screening of >34 000 minor asylum seekers universal screening for LTBI was advised, limiting additional radiographic screening to children ≥12 years old from certain high-incidence countries.

Our results show that robust logistics (time and place) and organisation (up-to-date administration), are indispensable for such screening. Further information is needed about factors causing only a minority of UMAs to be traced and tested.

**OA-27-670-23 Investigation of tuberculosis underreporting in the federal states of Germany**

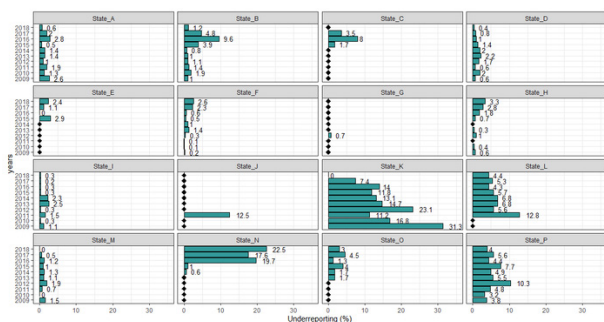
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**Background:** In 2018, the World Health Organisation estimated that approximately 3 million people (30%) were excluded from global new tuberculosis (TB) case counts due to underreporting or underdiagnosis. In Germany, from 2013-2017, TB underreporting was estimated to range from 3-9%. For targeted TB control however, aggregate national estimates alone are insufficient. Therefore, we examined the underreporting of TB from 2009-2018 at the subnational level in Germany.

**Design/Methods:** Record-linkage of two anonymised cases-based data sources (national TB notification data and antibiotic resistance surveillance data from voluntarily participating laboratories) was followed by a capture-recapture analysis by year (2009-2018) and German federal state.

**Results:** Median TB incidence in Germany was 5.5 per 100,000 population in the 10-year period. The median by federal state ranged from 3.4 to 10.1 per 100,000 population. Underreporting varied between and, over time, within federal states (Figure). Median of underreporting over time between states ranged from 0.3% to 13.6%.

However, underreporting was generally low and stable over time for most states, which included those most densely populated. Two states showed marked variation over time, but are sparsely populated so this equates to relatively few missed cases absolutely (n≤50)(Figure).



[Figure. Estimated underreporting (%) by federal state in Germany. It was not possible to estimate the underreporting if there was no data in one of the data sources (marked by ♦). Federal states were anonymised using identifiers.]

**Conclusions:** We identified some differences in TB underreporting by state and variation within state over time. However, there were two limitations. First, the analysis was limited by the use of two data sources, which increases uncertainty around the estimates. Second, missing data for certain years in some states prevented estimation of underreporting for that year. Overall, these preliminary findings underline the importance of subnational analyses to allow for targeted improvements in TB reporting.

### OA-27-671-23 Tuberculosis Source Investigation in the Netherlands - is it Effective?

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**Background:** WHO recommends tuberculosis (TB) source investigation (SI) for all children identified with TB. The goal of SI is to detect unidentified source patients or co-infected TB patients and prevent further transmission. Yet there is limited published evidence on the effectiveness of SI. We determined the TB and latent TB infection (LTBI) yield of SI in the Netherlands, where SI is performed around TB patients with a likely recent infection whose source of infection is unknown.

**Design/Methods:** Aggregated numbers of contacts tested and identified with TB and LTBI are recorded around each TB patient notified in the Netherlands TB registers (NTR). Data from SI performed around index patients with extrapulmonary or culture-negative pulmonary TB notified from 2006-2016 were included in the analysis. We compared the yield of TB and LTBI among subgroups of index patients using a generalized estimating equations logistic regression model.

**Results:** SI was performed around 2,484 /5299 (47%) notified index patients with extrapulmonary or culture-negative pulmonary TB. In total 11,420 contacts were tested for TB of whom 8129 (71%) also for LTBI. The overall TB yield was 0.40% (n=46), and 0.50% (n=44)

among close contacts. The yield of LTBI was 7.2% (n=582); 8.3% (n=501) among close, 3.9% (n=77) among casual and 3.6% (n=4) among community contacts. The yield of TB was higher among contacts of children than adults (OR=5.4(95%CI:2.4-12.4)). The yield of LTBI was higher among contacts of non-Dutch patients (aOR=2.3(95%CI:1.6-3.4) and lower for contacts of persons belonging to a marginalized group (aOR=0.18(95%CI: 0.04-0.90).

Index patient characteristics	N index patients	N contacts tested	TB yield (%)	OR (95% CI)	p-value	N contacts tested for LTBI	LTBI yield (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
SI performed	2484	11420	46 (0.4%)			8129	582 (7.2%)				
Age ≤14	98	1123	17 (1.5%)	5.4 (2.4-12.4)	<0.001	953	95 (10.0%)	1.5 (0.86-2.7)			0.15
>14	2386	10297	29 (0.3%)	1		7176	487 (6.8%)	1			
Sex Male	1203	5555	22 (0.4%)	1		4100	289 (7.0%)	1			
Female	1281	5865	24 (0.4%)	1.0 (0.49-2.2)	0.93	4029	293 (7.3%)	1.0 (0.78-1.3)			0.87
Origin Dutch	454	2784	7 (0.3%)	1		2410	90 (3.7%)	1			1
Non-Dutch	2030	8636	39 (0.5%)	1.8 (0.8-4.0)	0.15	5719	492 (8.6%)	2.4 (1.6-3.5)	<0.001	2.3 (1.6-3.4)	<0.001
Marginalized group No	2459	11298	46 (0.4%)			8024	581 (7.2%)	1			1
Yes	25	122	0 (0.0%)			105	1 (1.0%)	0.13 (0.03-0.54)	0.005	0.18 (0.04-0.90)	0.036

[Table.]

**Conclusions:** The yield of TB and LTBI was comparable to the yield among contacts of infectious TB patients notified in the same period (0.5% and 7.9% respectively). We conclude SI is an effective approach to identify potential sources of TB transmission in a low burden setting, particularly in children.

### OA-27-672-23 Evaluating tuberculosis transmission in a penitentiary system using customized MIRU-VNTR typing

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**Background:** Mycobacterial Interspersed Repetitive Units – Variable Tandem Repeats (MIRU-VNTR) 24 loci panel had been successfully implemented in Georgia, with Tuberculosis (TB) incidence of 80 per 100 000. Due

to cost and workload, in addition to phylogeographical distribution of Mtb strains and diverse discriminatory power of loci towards strain variation, we aimed to customize MIRU-VNTR 24 loci panel to Georgian population and validate the method for exploring transmission clusters in the cohort of the patients from penitentiary system.

**Design/Methods:** We used Hunter-Gaston Discriminatory indexes (HGDI) to assess and customize 10 high discriminatory loci for genotyping pulmonary TB samples from the penitentiary system collected from 2014 and 2015 in Georgia. Clusters were defined with double locus variation and we identified Mtb lineages using whole genome sequencing or TaqMan real-time PCR. Epidemiological metadata was linked to the genotyped clusters for identifying predictors of transmission.

**Results:** Customized MIRU-VNTR typing of 102 samples from penitentiary system revealed seventy-three (76.1%) cases distributed in eight clonal complexes and twenty-nine singletons. Discriminatory power of selected loci varied in context of Mtb lineages, while customized set covered highly sensitive loci for two lineages (Lineage 2 & 4) mainly distributed in Georgia. We found significant positive association between clustering and lineage 2 strains, in addition to drug resistant TB cases.

**Conclusions:** Our results strengthens the idea of the strain variation as a main indicator for choosing appropriate methodology. Although, we focused on customization of MIRU-VNTR typing for the Georgian population, the findings may well have a bearing on exploration of clusters in penitentiary system. Giving a relative knowledge regarding the transmission groups, focusing on strain diversity and drug-resistant TB could produce valuable details that account more for transmissions in prisons. A key policy priority should be to implement typing tool for the long-term surveillance incarcerated patient.

## OA-28 New and old tests for latent TB infection

### OA-28-673-23 Systematic review on the diagnostic performance of specific skin test for latent TB infection compared to interferon-gamma release assays and tuberculin skin tests

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**Background:** To reduce TB incidence globally, treatment of latent TB infection (TBI) is crucial. Widely implemented diagnostic tests are the tuberculin skin test (TST) and interferon gamma release assay (IGRA). Newer skin tests have been developed to improve test specificity and scalability; C-Tb (Serum Institute of India); Diaskintest (Generium); ESAT6-CFP10 (Anhui Zhifei Longcom). This systematic review synthesises current evidence on their performance.

**Design/Methods:** Searches were conducted in English (Medline, Embase), Russian (e-library) and Chinese (Chinese Biomedical Literature Database; China National Knowledge Infrastructure) databases. Included studies reported performance of tests alone or against comparator; these were evaluated against a hierarchy of pre-defined reference standards for TBI. Pooled estimates were obtained via random-effects meta-analyses. Study quality was assessed using QUADAS-2. (PROSPERO registration: CRD42019135572).

**Results:** 1,512 English, 370 Russian and 0 Chinese language abstracts were identified; 244 full texts reviewed; 31 studies included (25 Diaskintest (n=6933); 5 C-Tb (n=2744); 1 ESAT6-CFP10 (n=144); Table 1). No longitudinal or studies comparing index test performance were identified. Study quality varied, with medium to high risk of bias. Pooled Diaskintest results: agreement

with IGRA 94.2% (90-96.8%); 97.4% with TST (96.4-98.1%) (age <18); sensitivity 69% (57-79%) and 88% (78-94%) (cut-offs: any induration; 5mm, respectively). (Data insufficient for specificity estimates). Pooled C-Tb results: agreement with IGRA 79.6% (76.3-82.6%); with TST 81.0% (78.1-83.7%); sensitivity 73% (67-79%); specificity 98% (94-99%). A single ESAT6-CFP10 study found sensitivity 86% (67-95%); specificity 93% (69-99%). Sensitivity analyses by HIV status and TB diagnostic method did not differ significantly from primary analyses.

	DST <sup>AI</sup>	DST <sup>5mm</sup>	C-Tb
<b>Total number included</b>			
Children < 18 years	3,298	58	920
HIV-infected	88	86	532
Active TB	1,769	240	566
<b>Pooled agreement IGRA % (95% CI)</b>	94.2 (90-96.8)	n/a	79.6 (76.3-82.6)
Children < 18 years	76.4 (72.7-80.1)	n/a	n/a
HIV-infected	n/a	n/a	80.4 (73.6-85.8)
Active TB	96.7 (92.4-98.6)	n/a	79.6 (76.3-82.6)
<b>Pooled agreement TST % (95% CI)</b>	n/a	29.4-81.25**	81.0 (78.1-83.7)*
Children < 18 years	97.4 (96.4-98.1)	n/a	n/a
HIV-infected	69.6-84.9**	n/a	80.8 (75.6-85.2)*
Active TB	69.6-98.9**	n/a	76.4 (71.3-80.8)*
<b>Pooled sensitivity % (95% CI)</b>	69 (57-79)	88 (78-94)	73 (67-79)
Children < 18 years	98-100	n/a	n/a
HIV-infected	n/a	n/a	n/a
<b>Pooled specificity % (95% CI)</b>	n/a	n/a	98 (94-99)
<b>Gradient of positivity in contacts of active cases</b>	Present	Present	Present
<b>Adverse events (%)</b>	Not reported	Not reported	30.9
Mild			

TST cut off used 5mm, unless otherwise indicated

TST used: TST PPD-L for Diaskintest, TST PPD-RT23 for C-Tb and ESAT6-CFP10

DST<sup>AI</sup> – Diaskintest using any induration cut off

DST<sup>5mm</sup> – Diaskintest using 5mm cut off

n/a – insufficient data

\*Stratified TST cut off used – 5mm in BCG unvaccinated or HIV-infected, 15mm in BCG vaccinated

\*\*Insufficient data to pool therefore range of point estimates presented

[Table 1. Summary of test performance against reference standards]

**Conclusions:** C-Tb, Diaskintest and ESAT6-CFP10 appear to perform similarly to IGRA and TST. However, more studies are needed to evaluate test performance against all reference standards, address heterogeneity in study design, and enable between-test comparison.

## OA-28-674-23 An evaluation of community-based TB infection testing using the QuantiFERON-TB Gold Plus assay and preventive treatment linkage in Ho Chi Minh City, Viet Nam

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**Background and challenges to implementation:** Viet Nam has developed an ambitious plan to end TB by 2030, which includes the scale up of TB infection testing and TB preventive treatment (TPT).

**Intervention or response:** Friends for International TB Relief piloted the integration of TB infection testing using the QuantiFERON-TB Gold Plus (QFT) assay at mobile chest X-ray (CXR) screening events in Ho Chi Minh City, Viet Nam. Contacts of TB patients, health workers and community members with TB symptoms were mobilized, examined by CXR and had blood drawn. People with an abnormal CXR were tested on Xpert. Blood specimens were transported every day at noon to the Provincial Lung Hospital to process samples within six hours after specimen collection. QFT(+) individuals in whom active TB was ruled out were eligible for TPT using nine months of isoniazid (9H). Routine TB care staff monitored patient treatment and follow-up.

**Results/Impact:** 4,956 people were tested with QFT and 1,652 (33.3%) had QFT(+) results. The indeterminate rate was 0.8% (41/4,956). Males, older people and contacts were more likely to be QFT(+). Adjusting for age and gender, health workers and contacts were less likely to be QFT(+) than community members. 1,019 people were started on 9H (61.6% of those eligible). The median time between QFT result and TPT initiation was 16 days (3-147). Currently, 123 people had fully completed their 9H treatment (12.1%) and another 721 had completed between 3-8 months and were still on treatment (70.8%).

**Conclusions:** This pilot showed it was feasible to use the QFT assay at the community level. Although contacts are eligible for TPT after a clinical evaluation in WHO guidelines, just 37.8% were QFT(+) in this pilot, highlighting the utility of TB infection testing. Future studies should evaluate whether shorter TPT regimens can increase TPT acceptability and reduce health system costs.



**OA-28-675-23 The magnitude of interferon gamma release assay response among children with household contact in a high-burden setting is associated with tuberculosis exposure and active disease**

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**Background:** The clinical utility of quantitative interferon gamma (IFN $\gamma$ ) responses is unknown, especially in children. We assessed the association between the magnitude of IFN $\gamma$  response and degree of Mycobacterium tuberculosis (*M.tb*) exposure, and tuberculosis infection and disease in children.

**Design/Methods:** Cross-sectional analysis of child household contacts ( $\leq 15$  years) with recent exposure to an adult with bacteriologically confirmed pulmonary TB, enrolled 2007-2012 in Cape Town, South Africa. IFN $\gamma$  values were reported as IFN $\gamma$  concentration and IFN $\gamma$  spot forming units (SFU) for the QuantiFERON-TB Gold In-Tube (QFT-GIT) and T-SPOT.TB, respectively. An established *M.tb* contact score was used to categorize children by degree of exposure. TB phenotype was categorized as having TB disease, *M.tb* infection (positive tuberculin skin test), or no *M.tb* infection/TB disease. Random effects linear regression analysis was used to investigate the relation between the *M.tb* contact score, TB clinical phenotype, and IFN $\gamma$  response as outcome, adjusting for clinically and epidemiologically relevant covariates.

**Results:** We analyzed data from 669 child contacts (median age 63 months; IQR=33-108). Higher IFN $\gamma$  responses were associated with increasing level of *M.tb* exposure: a one-unit increase in contact score was associated with an increase of IFN $\gamma$  0.59 IU/ml (95% CI=0.43-0.75), and IFN $\gamma$  SFU 2.12 counts (95% CI=1.28-2.96). In adjusted analyses, IFN $\gamma$  response was significantly lower among children with *M.tb* infection compared to children with TB disease (b=-1.41, 95% CI=-2.80 -0.02) for QFT-GIT, but not for T-SPOT.TB. This association was strongest among children age 2-<5 years (b=-2.32, 95% CI=-4.25-0.40) and absent among age <2 years.

**Conclusions:** The magnitude of IFN $\gamma$  response correlated with the degree of *M.tb* exposure using QFT-GIT and T-SPOT.TB, and TB clinical phenotype, including TB disease, using the QFT-GIT. This suggests that IFN $\gamma$  values are useful in not only estimating *M.tb* infection risk, but may also support the diagnosis of TB disease in young children.

**OA-28-676-23 Correlation between Monocyte to Lymphocyte Ratio (MLR) and tuberculin skin test (TST) positivity among ART-naïve adults**

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**Background:** The Tuberculin skin test (TST) is used to identify individuals at increased risk of developing TB but poses major logistical challenges. The blood Monocyte to Lymphocyte ratio (MLR) could be an alternative as extremes in MLR have been associated with an increased TB risk in adults starting ART.

**Design/Methods:** A differential white blood cell count (including monocytes and lymphocytes) was performed in addition to a routine TST in adults presenting for pre-ART care in a primary care clinic in Johannesburg. Regression analysis and correlation tests were carried out to assess the association between TST positivity and MLR.

**Results:** Among the 229 participants with valid MLR results, 171 returned for TST reading of whom 51 (30%) were TST positive. Median monocyte count was 0.26 x 10<sup>9</sup> cells/L (IQR 0.21-0.35), median lymphocyte count was 1.52 x 10<sup>9</sup> cells/L (IQR 1.08-1.92), and median MLR was 0.18 (IQR 0.13-0.28). In multivariate regression analysis, higher CD4 count (>250 cells/mm<sup>3</sup>) was the only variable associated with a positive TST (AOR 3.10, 95% CI 1.37-7.35, adjusted for MLR and lymphocyte count). In people with a high CD4 count (>250 cells/mm<sup>3</sup>), MLR was not associated with TST positivity (r=0.44, p=0.38). In the people with CD4  $\leq 250$  cells/mm<sup>3</sup>, TST positivity declined linearly (r=-0.68, p=0.03) with MLR (median 0.22, IQR 0.17-0.43). A MLR cutoff of <0.40 would have a sensitivity of 92% (95% CI 64%;100%) and a specificity of 31% (95% CI 20%;43%) to predict a positive TST in the people with low CD4 count ( $\leq 250$  cells/mm<sup>3</sup>).

**Conclusions:** TST positivity decreased significantly with increasing MLR, but only among those with lower CD4 counts. Considering the TST-related logistical challenges and impaired TST sensitivity in this population, future research is needed on MLR as a useful surrogate marker to identify people eligible for preventive TB therapy.

### OA-28-677-23 Novel strategies for tuberculin skin testing at primary care clinics: an economic evaluation

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**Background:** A tuberculin skin test (TST)-guided Isoniazid Preventive Therapy (IPT) strategy for people living with HIV poses major implementation challenges with regards to human resources and patient costs. Task-shifting, fast-tracking and patient TST self-reading could be innovative ways to increase the feasibility of TST in low resource countries.

**Design/Methods:** For an empirical costing of TST program (including placement and reading) and patient-level costs, we followed the WHO-CHOICE methodology and measured costs prospectively using an “ingredients” approach through a combination of budgetary review, interviews, and direct observation in a primary care clinic in Johannesburg. To generalize the net cost savings of a self-reading and task-shifting strategy from a provider perspective, a simulation was performed for 5 other countries with important differences in income (lower and upper middle- or high-income countries), personnel costs, and latent TB burden (9 to 26%).

**Results:** Total TST program cost (reading and placement) was 1632 I\$ per 100 patients and majority (84%) was patient costs. Employing fast-tracking and task-shifting of TST reading, reduced the overall program costs to 1241 I\$ per 100 patients as the provider reading cost per 100 patients reduced from 109 I\$ to 26 I\$ and the patient-level reading costs per 100 patients reduced from 683 I\$ to 375 I\$ considering a TST prevalence of 26%. Implementing a fast-track, task-shifting and self-reading approach, would reduce the provider costs of the TST reading by minimum 78% in all countries simulated as compared to the standard of care. Those savings could lower the total cost of the TST program from a provider perspective up to 40%.

**Conclusions:** A TST self-reading policy, where only those patients with self-determined presence of any induration are asked to return for TST reading, fast-tracked and assessed by a trained lower cadre health care worker, could greatly reduce the human resource and patient costs of TST.

### OA-28-678-23 TB screening in health care workers in Mozambique. Where we are?

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**Background and challenges to implementation:** Tuberculosis causes morbidity among millions of people every year, and has become the deadliest infectious disease among people living with the HIV, all over the world. In 2019, Mozambique reported 97,111 TB cases all forms, which corresponds to a notification rate of around 340 / 100,000 per populations and in this period, we had 41 441 HCWs.

**Intervention or response:** A retrospective analysis of 2019 nationwide TB screening data of health workers' and well-being consultations was carried out. Data were extracted from the records books of these consultations and descriptive statistical analysis was performed to determine the occurrence of TB infection in HCW.

**Results/Impact:** During this period all the districts reported HCWs TB screening activities. A total of 20 833 HCWs (50%; n=41 441) were screened for TB. Of the HCWs screened, 334 were diagnosed TB which corresponds to an incidence rate of 806 cases/100 000 per HCWs. Of these HCWs diagnosed with TB, 212 (63.5%) were bacteriologically confirmed. Among the positive cases, 145 (43%) were HIV positive. We found 60 (8.0%) cases of DR-TB in this populations during this period. The nurses (n=119; 35,6%), auxiliary staff 3(n=87; 26%) and administrative staff (n=51; 15,3%) were the professional categories with the most TB cases reported.

**Conclusions:** In this study we found that only 1/2 of the cases of HCWs are screened for TB. And the TB cases on this risk group are 2 times higher than in the general population. As HCWs are in the high risk group for TB and HIV, more concerted action plan should be taken in this risk group and mainly in the nurses, service assistants and in the administrative staff. Actions aimed at better access to services, systematic screening, active case finding are necessary in this population, in order to reach the goals of the Global Strategy for Tuberculosis elimination.

### OA-28-679-23 Identification of barriers and facilitators of tuberculosis contact investigation in Cali, Colombia

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**Background and challenges to implementation:** To identify barriers to and facilitators of tuberculosis (TB) contact investigation in Cali, the third largest Colombian city, by examining the perceptions and lived experiences of stakeholders.

**Intervention or response:** In this cross-sectional qualitative study combining human-centered design, social science methods, and a knowledge-growing strategy, we conducted three activities involving different stakeholders: a) focus-group discussion (1) with program coordinators and health-care workers, b) in-depth interviews with index TB patients (8) and household contacts (16), and c) context mapping sessions (6), with purposive selection of contacts. After consent, activities were audio-recorded and professionally transcribed. Using grounded theory, we generated and applied codes and categories to emergent themes until we achieved data saturation for each activity.

**Results/Impact:** Common barriers are associated with low access to households (violence and lack of transportation into informal settlements, inaccurate data recording), deficient uptake of standardized guidelines, low quality of training for health-care workers; previous negative experiences and lack of confidence to the health-care system were perceived by patients and their contacts, poor communication between patients and health-workers during the visit, lack of economic resources and excessive paper-work were the final barriers for contacts' evaluation. Significant facilitators included resourcefulness, empathy and delivery of clear information about TB from health-care workers; whilst family and social support and interest in remaining healthy was key for patients and contacts.

**Conclusions:** Household contact investigation in Cali could be improved by 1) enhancing personal skills and training of health-care workers with the use of standardized TB educational materials, 2) facilitating access to households by involving community leaders and implementing digital communication tools, and 3) defining a step by step attention route for patients and contacts, that involves a standardized data recollection system.

### OA-29 Who pays the cheque? The economic burden of TB

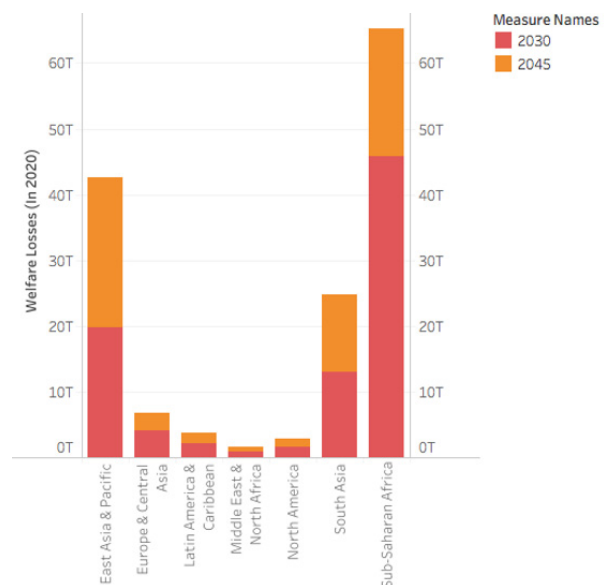
#### OA-29-680-23 Assessing the economic impact of TB mortality in 165 countries: what it will cost if we don't achieve the End TB targets

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**Background:** We aim to determine the economic dividend of achieving the End TB mortality target by 2030. We estimate as a 'Cost of Inaction', the welfare penalty that will be borne by countries over the next three decades, in the event that the target is not met by 2030 as intended.

**Design/Methods:** We estimated cause-eliminated life expectancy in 165 countries, from 2020-2050, if TB deaths fell by 2% annually. We estimated the life expectancy gain if the End TB mortality target was met in 2030 versus 2045. To do so, we monetized life expectancy gains employing the approach first employed in the Commission on Investing in Health. We stratified results by HIV status, multi-drug resistance and HIV burden, by WHO regions and by World Bank country income groups.

**Results:** If TB deaths declined at 2% annually from 2020-2050, 31,881,190 deaths result, giving rise to US\$281.08 billion in welfare losses. If the End TB mortality target was met in 2030, 16,164,765 deaths result, giving rise to US\$145.50 billion in welfare losses.



[Figure.]

Meeting the End TB target in 2030 eliminates US\$135.5 billion in welfare losses. If the End TB mortality target was not met until 2045, then 28,659,250 deaths would result, with 10,172 years in life expectancy losses and US\$ 245.70 billion in welfare losses. The 'Cost of Inaction' is therefore US\$100.74 billion. If TB deaths in people living with HIV (PLHIV) were excluded, losses reduce to US\$82.98 billion. Deaths in PLHIV contribute 17.63%. The Cost of Inaction was highest in East Asia (US\$38 billion), Sub-Saharan Africa (SSA) (US\$32.60 billion). When PLHIV are excluded, losses in SSA reduce to US\$19.0 billion, on par with South Asia.

**Conclusions:** Failure to achieve the End TB targets by 2030 will have devastating economic impacts on countries with high prevalence of HIV and TB, especially in SSA.

### OA-29-681-23 First national survey of the costs borne by households with tuberculosis in DRC, 2019

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**Background:** Free TB care official policy in DRC and recent progress with Universal Health Coverage access and financial protection levels are seemingly insufficient to remove barriers to TB care access and adherence. As the economic burden borne by TB patients was unknown at national level, the Tuberculosis program seek to establish a baseline survey to monitor the proportion of households experiencing catastrophic costs, understand the composition, magnitude of such cost and worst affected.

**Design/Methods:** A national survey with retrospective data collection and projection was administered in 2019 to 1118 participants in 43 clusters. Each patient was interviewed once on costs, time loss, coping measures, income, annual household expenditure and asset ownership. Total costs (including indirect costs measured as a valuation of time loss, human capital approach) were expressed as a percentage of annual household expenditure. WHO method and reporting standards were followed.

**Results:** 56% of households affected by TB or MDR-TB in DRC, experienced costs that were above 20% of their annual household expenditure. Mean patient costs

amounted to \$399 (\$328- \$471) and \$1224 (\$762- \$1686) per episode of TB and MDR-TB respectively. The largest drivers of mean costs are post-diagnosis non-medical costs (travel, food, nutritional supplements and accommodation) and indirect costs. Risk of catastrophic costs increased with hospitalization, drug resistance level and poverty. 49% of households resorted to dissaving strategies to overcome costs associated with the disease. 78% lost days of work, 23% lost their jobs and 48% experienced food insecurity. 94% of surveyed had no health insurance and 7.5% received social support (food or transportation).

**Conclusions:** Over half of TB affected households experience catastrophic costs, posing barrier to TB diagnosis and treatment. Based on results, programme and partners need to identify key areas for policy action and work towards a national policy guide on intervention to reduce TB patient costs.

### OA-29-682-23 Determinants of household catastrophic costs for tuberculosis care in Kenya

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**Background:** Despite free diagnosis and treatment for Tuberculosis (TB), the costs impose a significant financial burden on patients. Catastrophic costs (CC) cause impoverishment for affected households and are associated with negative treatment outcomes. To mitigate CC, there is need to identify those who are most at risk. This study sought to identify the determinants for CC among patients with drug-sensitive TB (DSTB) and their households in Kenya.

**Design/Methods:** The data was collected during the 2016 patient cost survey from a nationally representative sample (n=1071). Treatment related costs and productivity losses were estimated. Total costs exceeding 20% of household income was defined as catastrophic and used as the outcome. Poisson regression analysis was performed, to measure the association between selected patient characteristics and occurrence of CC.

**Results:** The proportion of CC among DSTB patients was 27% (n=294). Patients who incurred CC had higher productivity losses (median= 39 hours, IQR [20-104]), and total costs (median= USD 567, IQR [299-1,144]) compared to those without CC. The risk of CC was associated with low economic status: Adjusted Prevalence ratio (aPR) = 6.2 ,95% CI [4.0-9.7]) for the poor-

est quintile (Q1), aPR= 3.4, 95% CI [2.1-5.3]) for Q2 and aPR=2.4, 95% CI [1.5-3.9] for Q3. There is a dose-response relationship (proportion of CC= 6.8, 11.9, 18.4, 25.5 and 37.4% from the richest Q5 to the poorest (Q1). Other determinants include hospitalization (aPR= 2.8, 95% CI [1.8-4.5]) and delayed treatment (aPR= 1.5, 95% CI [1.3-1.7]). Less risk was associated with receiving care at a public health facility (aPR= 0.8, 95% CI [0.6-1.0]), and a higher BMI (aPR= 0.97, 95% CI [0.96-0.98]).

Univariable and multivariable regression of factors associated with CC

Variable (n=1071)	Prevalence Ratio (95% CI)	P value	Adjusted Prevalence Ratio (95% CI)	P value
Hospitalization (ref= not hospitalized)	3.1 (2.12-4.43)	<0.001	2.8 (1.76-4.53)	<0.001
Treatment delay (ref= <4 weeks)	1.6 (1.27-1.89)	<0.001	1.5 (1.26-1.73)	<0.001
Type of facility offering treatment (ref = private)	0.8 (0.62-0.98)	0.032	0.8 § (0.59- 0.95)	0.021
BMI±	0.98 (0.97-0.99)	<0.001	0.97 (0.96-0.98)	<0.001
Pre-TB Household income quintiles (ref= Quintile 5) ± Poorest	Q1 6.3 (3.88-10.29)	<0.001	6.2 (4.03-9.65)	<0.001
	Q2 3.40 (2.10-5.64)	<0.001	3.40 (2.12- 5.32)	<0.001
	Q3 2.5 (1.40-4.24)	0.002	2.4 (1.46- 3.91)	<0.001
TB type (ref=EPTB±)	0.8 (0.61-1.00)	0.050		

[Table.]

**Conclusions:** There are significant inequities in the occurrence of CC. There is need for social protection interventions to complement health system interventions for the most vulnerable patients.

### OA-29-683-23 Economic burden of tuberculosis in Tanzania: a national survey of costs faced by TB-affected households

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**Background:** Although tuberculosis (TB) care is free in Tanzania, TB-associated costs may compromise access to services, treatment adherence, and patients' outcomes. We assessed the economic burden of the disease on TB patients and their households and identified the main cost drivers of TB in Tanzania.

**Design/Methods:** We conducted a nationally representative cross-sectional survey using standard methodology recommended by World Health Organization. TB patients of all ages and with all types of TB from 30 clusters across the country were interviewed during July–September 2019. We used the human capital approach to assess costs and a threshold of 20% to determine the proportion of TB-affected households experiencing catastrophic cost. Data were analyzed using descriptive statistics and logistic regression accounting for the survey design.

**Results:** Of 777 TB-affected households, 45% faced catastrophic costs due to TB. This proportion was higher (80%) among households of patients with drug-resistant TB. Independent predictors of catastrophic costs included hospitalization (adjusted odds ratio [aOR]=34.9 [95% confidence interval (CI):12.5–146.11]), living in semi-urban (aOR=1.6 [95% CI:0.9–2.5]) and rural areas (aOR=2.6 [95% CI:1.8–3.6]), having drug-resistant TB (aOR=3.4 [95% CI:1.2–10.9]), and facility-based directly-observed treatment (aOR=7.2 [95% CI:2.4–26.6]). Main cost drivers included income loss due to accessing TB services (34%), nutritional supplements (33%), and medical costs (15%). Most income loss was associated with hospitalization (49%) and long and frequent travel times to pick up drugs (28%). Most patients (86%) reported worsening financial situations due to TB, and 53% took out a loan or sold assets to finance TB treatment.

**Conclusions:** We found that the economic burden for households due to TB in Tanzania is high; our findings support the results from other surveys recently conducted in Africa. Innovative approaches to minimize household costs due to TB disease could improve access to care, patient adherence and outcomes.

### OA-29-684-23 Direct medical costs and out-of-pocket expenditures on tuberculosis treatment in three regions of China

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**Background:** As one of the major targets in End Tuberculosis (TB) Strategy, TB-affected families facing catastrophic costs due to TB should be completely eliminated before 2035. This study aimed to understand the direct medical costs on TB treatment, and to evaluate the economic burden caused by out-of-pocket expenditures on TB patients in China.

**Design/Methods:** Smear-positive TB patients diagnosed between June 2017 and June 2018 in TB designated clinics in three regions of China were included, excepting multidrug-resistant TB patients. Medical costs, demographic and clinical information were extracted from hospital information system. out-of-pocket expenditures, mainly consisting of the costs on additional examinations and medicines for comorbidities and drug-induced adverse effects, exceeded 40% of annual household income was defined as catastrophic cost.

**Results:** A total of 245 smear-positive TB patients were included, and were divided into inpatient (n=112) and outpatient (n=133) groups to evaluate the costs during respective treatment periods. Median durations for inpatient and outpatient treatment were 0.3 and 6.0 months, respectively. Comorbidities and adverse effects were reported in 61 (54.5%) and 52 (46.4%) patients from inpatient group while in 67 (50.4%) and 107 (80.5%) patients from outpatient group. During inpatient treatment, the median direct medical cost was 5,383 Chinese Yuan (CNY), of which out-of-pocket expenditures accounted for 23.8%. As a result, 13.4% of the TB-affected families faced catastrophic costs. For patients receiving outpatient treatment, the median direct medical cost was 2,554 CNY while out-of-pocket expenditures accounted for 49.9%, mainly due to the high incidence of adverse effects. The proportion of those TB-affected families facing catastrophic costs was 2.3%.

	Inpatient group (n=112)	Outpatient group (n=133)
Age, years (mean ± standard deviation)	52.8±16.1	49.6±12.7
Male (%)	91 (81.3)	108 (81.2)
Medical insurance (%)	110 (96.8)	125 (94.0)
Drug-induced adverse effects (%)	52 (46.4)	107 (80.5)
Comorbidities (%)	61 (54.5)	67 (50.4)
Treatment duration, months (median, interquartile range)	0.3 (0.2, 0.5)	6.0 (6.0, 9.0)
Direct medical costs, Chinese Yuan (median, interquartile range)	5383 (3669, 7836)	2554 (1789, 4129)
Out-of-pocket expenditures, Chinese Yuan (median, interquartile range)	1283 (519, 3027)	1274 (889, 2022)

Table 1. Demographic characteristics, clinical features and medical costs of enrolled tuberculosis patients

**Conclusions:** Medical costs during inpatient treatment resulted in more than 10% of TB-affected families facing catastrophic costs while outpatient treatment was observed with high proportion of out-of-pocket expenditures. To achieve End TB targets in China, there is an urgent need to enhance financial support.

### OA-29-685-23 Catastrophic costs associated with diagnostic cascade and treatment of tuberculosis among patients treated at a public health center in Rio de Janeiro, Brazil

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**Background:** Poor socioeconomic conditions increase the risk for tuberculosis (TB) infection, reactivation, and maintenance of TB in the community. We conducted a prospective study involving patients undergoing treatment for TB in a municipal health center in the metropolitan region of Rio de Janeiro aiming to assess the direct, indirect and catastrophic costs incurred for patients with TB.

**Design/Methods:** Analyzes were done using the questionnaire endorsed by the World Health Organization in the "Tuberculosis Patient Cost Surveys: a Hand-

book” 2017. The parameters considered were: socio-demographic characteristics, time to diagnosis, patients individual income before and after TB treatment, total family costs, coping strategies, social consequences and catastrophic costs, defined as the total cost of TB care exceeding >20% of the annual family income. Poverty line was defined as per capita income up to \$ 1.9/day, updated by the latest Purchasing Power Parity (World Bank).

**Results:** 110 patients with drug-sensitive TB (DS-TB) and 10 with drug-resistant TB (DR-TB) were recruited; 69% were males and 60% were under 45 years-old. Median time to diagnosis was higher among DRTB (17 vs. 11 weeks). Sixty-eight percent of families (82/120) faced catastrophic costs. Median total costs incurred during diagnostic and treatment cascade were higher in the group with DR-TB (\$ 5019,50 vs. \$ 3738,57) and 35% (42/120) of patients used coping strategies. Before illness, 5% (6/120) of individuals were below the poverty line, increasing to 28% (34/120) after end of TB treatment. The social consequences most reported by patients with TB were loss of work and social isolation.

**Conclusions:** A high percentage of patients faced catastrophic costs, confirming the direct relationship between TB and the social determinants of health. Our results highlight the need for investments in social protection strategies for TB patients, without which the goal of eliminating TB in Brazil will not be achieved.

### OA-29-686-23 Why Cepheid Xpert MTB/RIF and SARS-CoV-2 cartridges should not be sold to low- and middle-income countries at more than \$5 per test

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**Background and challenges to implementation:** In 2012, WHO, on behalf of Unitaid, signed a 10-year buy-down agreement for \$11,100,000 with Cepheid to reduce the price of the Xpert MTB/RIF cartridges (Cepheid, USA) to \$9.98 ex works for the public sector in 145 low- and middle-income countries (LMIC). We report an estimated cost of goods (COGS) analysis of the MTB/RIF and HIV cartridges and extrapolated to the SARS-CoV-2 cartridge now priced to LMIC at \$19.80.

**Intervention or response:** COGS, defined as the direct costs of production including materials and labor, of the Xpert MTB/RIF Standard, Xpert HIV Viral Load and Xpert MTB/RIF Ultra were analyzed by Cambridge Consultants (UK) in 2012, 2015 and 2018. A teardown analysis was used to understand the cartridge architecture and differences between variants followed by COGS calculations for plastics, reagents, assembly, packaging and royalties.

**Results/Impact:** At annual sales volumes of 1 million cartridges, the estimated COGS of the MTB/RIF standard and Ultra are \$8.53 and \$8.72, respectively. COGS estimates decrease to \$4.96 at 10 million sales volumes and to \$2.96 when all royalties are considered expired. COGS for the HIV viral load (VL) cartridge is estimated at \$10.91 per test at 1 million sales volumes. Cepheid leveraged the Xpert Xpress Flu/RSV Cartridge to develop the SARS-Cov-2 cartridge with no difference in design except the reagents for specific SARS-CoV-2 targets, for which sequences are open source. As such, manufacturing costs can be pooled across different diseases cartridges and further decreases production cost estimates through volumes of scale.

**Conclusions:** COGS data show that at current sales volumes, exceeding 10 million per year, MTB/RIF cartridges can be sold with 20% profit between \$5 and \$7 including service and maintenance (\$1 per test), allowing LMICs to upscale TB testing. There is no COGS-based evidence why the viral cartridges, including the SARS-CoV-2 cartridge, should be priced higher.

### OA-29-687-23 The cost of tuberculosis contact investigation in Uganda

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**Background:** Tuberculosis (TB) contact investigation is not implemented to scale and with fidelity especially in Low and Middle-Income Countries (LMICs) because the cost is said to be prohibitive. We set out to determine the unit cost of TB contact investigation in Uganda, a low-income but high TB prevalent country in relation to its Gross Domestic Product (GDP).

**Design/Methods:** We used the Activity-Based Costing (ABC) method to develop a costing model for TB Contact Investigation. TB contact investigation was broken down into salaries, meals, and incidental expenses, supplies and consumables, MTB/RIF GeneXpert costs, and training costs. Data from 12 Ugandan hospitals (11 Regional Referral & 1 District) was collected retrospectively, for the period April to September 2017. The data were collected from program records, databases, and interviews with frontline health workers. All the total costs required to perform TB contact investigation from the health care perspective were considered. The unit cost per TB case diagnosed by TB contact investigation was computed using the total cost and number of patients detected. This unit cost was then compared to Uganda's GDP per capita for 2017 (\$631.52).

**Results:** During the study period, there were 454 index TB cases and 2707 household contacts. Presumptive TB cases were 31% (830/2707) of the contacts. Of these,



86% (718/830) were tested and 38 (5.29%) were diagnosed with TB at a cost of USD \$ 33,3478. The unit cost of each case diagnosed was \$877.57, and the percentage unit cost to GDP was 1.45%.

**Conclusions:** The cost of conducting TB contact investigation is high relative to annual GDP per capita, limiting the scale-up of TB contact investigation services to lower-level health facilities in Uganda. These findings suggest a need to advocate for lowering the prices of the available diagnostics in order to lower the price of contact investigation.

## OA-31 TB epidemiology

### OA-31-688-23 Estimating the proportion of subclinical tuberculosis disease: definitions, associations and screening

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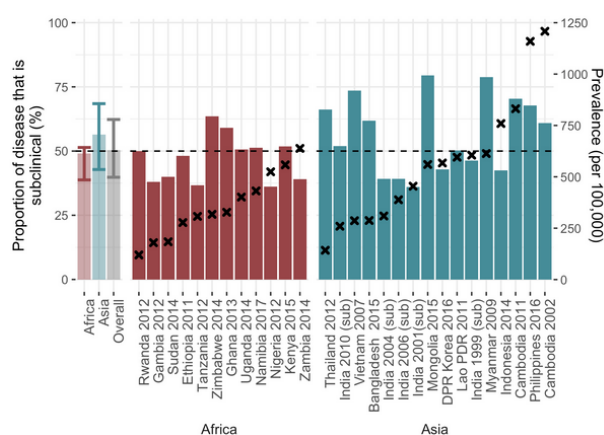
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**Background:** While it is known that a substantial proportion of individuals with tuberculosis disease (TB) present subclinically, usually defined as bacteriologically-confirmed, but negative via symptom screening interview, considerable knowledge gaps remain. Our aim was to review data from national and subnational TB prevalence surveys and generate a consistent definition and framework for subclinical TB, thus enabling an estimate of the proportion of TB that is subclinical, explore associations with overall burden and programme indicators, and performance of screening strategies.

**Design/Methods:** We extracted data from all publicly available prevalence surveys conducted since 1990, in which both symptom screening interview and X-ray

were performed on all eligible participants, and that reported the proportion of bacteriologically-confirmed cases by screening modality as well as the proportion of bacteriologically-confirmed cases that were negative on symptom screening.

**Results:** We included 23 national surveys and 5 subnational surveys, conducted in 23 countries across Africa and Asia, representing 36% of the global TB burden in 2018, and 57.5% (23/40) of all national level surveys completed since 1990. Between 36.1–79.7% (median 50.4%) of prevalent bacteriologically-confirmed TB was subclinical (Figure). No association was found between prevalence of subclinical and all bacteriologically confirmed TB, patient diagnostic rate or HIV prevalence (p-values, 0.21, 0.44, 0.46, respectively). Chest X-ray detected 89% (range 73–98%) of bacteriologically-confirmed TB disease, highlighting the potential of changing current TB case-finding policies.



[Figure.]

**Conclusions:** Where measured, around half of the prevalent infectious TB disease burden is subclinical, making it likely that ignoring this burden will diminish the impact of TB care and prevention efforts.

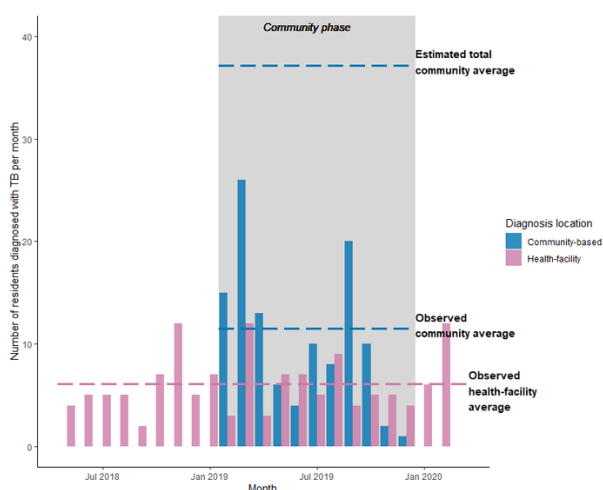
### OA-31-689-23 A high-resolution snapshot of subclinical TB via community-wide sputum testing in an urban Ugandan community

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**Background:** Highly sensitive diagnostic tests for tuberculosis (TB) have recently been developed but have not been used to comprehensively characterize TB at a community level.

**Design/Methods:** From February to November 2019, we offered sputum Xpert MTB/RIF Ultra (“Xpert”) testing to all adult residents of a well-defined community (population 34,000 adults) in Kampala, Uganda. We also enrolled all residents who were diagnosed with pulmonary TB through routine care at local health facilities. We compared all individuals with pulmonary TB to a representative sample of residents without TB using detailed interview, sputum TB culture, HIV testing, and serum C reactive protein (CRP).

**Results:** Of 12,301 residents contacted, 12,032 submitted sputum with a valid Xpert result. 113 tested positive for TB, including 71 (63%) trace positive. We estimated the prevalence of TB as 940 (95% confidence interval, 780-1130) per 100,000 adults; this estimate fell to 420 (320-550) after excluding individuals with unconfirmed, trace-positive Xpert.



[Figure. Timeline of health-facility and community-based case enrollment, and projected cases with 100% community-based screening coverage.]

We then compared four groups:

- (a) diagnosed in health facilities (n=95 enrolled);
- (b) community-based Xpert-positive (not trace, n=39);
- (c) community-based Xpert-trace-positive (n=63); and
- (d) individuals without TB (n=137).

We observed a spectrum of disease across these groups in terms of chronic cough (93%/77%/33%/18%), any TB symptom (99%/87%/60%/38%), CRP (75th percentile 101/28/6/4 mg/L), HIV (38%/13%/11%/10%), and history of TB treatment (24%/5%/8%/3%). Compared to testing at home, other community testing locations yielded a higher proportion of positive results (1.3% vs 0.8%) and identified a TB-positive population that was more predominantly male (80% vs 42%), had higher CRP levels (median 4.1 vs 2.5 mg/dL), and endorsed more chronic cough (62% vs 39%).

**Conclusions:** Population-wide use of Xpert Ultra identified a high prevalence of undiagnosed TB in the community, with different clinical features than TB diagnosed routinely in health facilities.

### OA-31-690-23 Methods and challenges of National TB Prevalence Surveys in Asia and sub-Saharan Africa: a systematic review

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**Background and challenges to implementation:** National TB Prevalence Surveys (TBPS) provide valuable information to policy makers and National TB Programs about TB burden and missing cases. However, TBPS can be challenging, especially in TB-endemic low- and middle-income countries (LMICs).

**Intervention or response:** We reviewed 28 World Health Organisation (WHO) TBPS reports from Asia (n=14) and sub-Saharan Africa (n=14), published after 2000. All surveys were population based and followed WHO guidance. All surveys used a TB symptom screening questionnaire and chest radiograph to identify people with suspected TB disease. Acid Fast Bacilli (AFB) smear (25/28, 89%), fluorescence microscopy (17/28, 61%), and mycobacterial culture (27/28, 96%) were used to diagnosed TB, with most post-2010 surveys also using GeneXpert (14/28, 50%).

**Results/Impact:** Several domains of TBPS challenges were identified and are summarized in Table 1.

Domain	Challenges/limitations	Possible Solutions
Under recruitment	<ul style="list-style-type: none"> <li>Under-estimation and recruitment of cases due to certain groups not meeting TBPS inclusion criteria including children, people with clinically and not microbiologically diagnosed TB, and those with extrapulmonary TB</li> </ul>	<ul style="list-style-type: none"> <li>Tuberculin survey in children needs to be considered alongside TBPS</li> <li>Widening of TBPS inclusion criteria in order to determine the exact burden of tuberculosis in the country</li> </ul>
Under representation	<ul style="list-style-type: none"> <li>Low participation in urban compared to rural areas, especially in young, working males</li> <li>Reliance on self-reported TB risk factors such as diabetes and HIV</li> <li>Minimal data collected relating to social determinants and no linkage of TBPS to other relevant national databases (e.g. employment, poverty, social protection)</li> </ul>	<ul style="list-style-type: none"> <li>Social mobilization and advocacy can be helpful to increase awareness and participation of all groups in the survey</li> <li>Social and health risk factors for TB disease should be included in the screening questionnaire or linked to national databases (e.g. Brasil links TB registry and social protection databases)</li> </ul>
Diagnostic	<ul style="list-style-type: none"> <li>Reliance on low-sensitivity sputum smear to diagnose TB prior to 2011</li> <li>Long and complicated procurement process for digital X-ray machines and associated logistics issues of maintenance</li> <li>Technical issues with chest radiography in the field (e.g. malfunctioning chest radiograph machine) and interpretation of results</li> <li>Impact of different diagnostic algorithms on yield of TB cases</li> </ul>	<ul style="list-style-type: none"> <li>Molecular diagnostic technology and digital X-ray need to be promoted in TPS</li> <li>A robust procurement plan needs to be developed and initiated early to avoid delays</li> <li>Modelling could support development of locally-appropriate and context-specific TB diagnostic algorithms for TBPS</li> </ul>
Logistic	<ul style="list-style-type: none"> <li>Geographical and topographical limitations to reaching participants (e.g. mountains/river); natural disasters including flooding, earthquakes, and landslides</li> <li>Security challenges including internal armed conflicts and threats to staff</li> <li>High turnover of field staff</li> <li>Delayed domestic funding which led to delays in procurement of diagnostics</li> </ul>	<ul style="list-style-type: none"> <li>An alternative plan might be supportive to manage the survey during conflict, natural calamities and transportation of logistics in geographically difficult areas</li> <li>Staff training and motivation plan is needed to retain skilled staff, which could be coupled with incentives</li> </ul>
Data Management	<ul style="list-style-type: none"> <li>Difficult to manage the data collected using paper-based systems (e.g. entering, coding, cross-checking, and tabulating data)</li> <li>Storage of data archive for many years</li> </ul>	<ul style="list-style-type: none"> <li>Paperless data collection system to be promoted, which would also enhance cross-linkage of TBPS survey data with relevant databases</li> </ul>

[Table 1.]

They included:

1) under-recruitment in urban settings (4/28, 14%) and exclusion of children and people with extrapulmonary or clinically-diagnosed TB (28/28, 100%);

2) under-representation of risk groups due to lack of complementary data collection concerning social determinants and reliance on self-reporting of TB risk factors including HIV and diabetes (28/28, 100%);

3) diagnostic limitations including reliance on low-sensitivity smear testing (14/28, 50%) and impaired laboratory capacity;

4) logistical implementation constraints including lack of funding and security issues; and,

5) issues with data management, especially with paper-based data collection (4/28, 14%).

**Conclusions:** Asian and African LMICs planning to conduct TBPS should focus on addressing potential modifiable challenges including: garnering adequate funding and promoting a sustainable workforce; developing context- and resource-specific diagnostic algorithms to improve TB yield; social mobilization and awareness campaigns to improve participation, including of hard-to-reach groups; expanding inclusion criteria to children and non-microbiologically confirmed TB cases; better linkage with socioeconomic and health data; and paperless data collection and management tools.

### OA-31-691-23 Trends in molecular epidemiology of drug resistant tuberculosis in Estonia

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**Background:** Estonia is among the most affected by tuberculosis (TB) in the World Health Organization European Region. The country was in the list of 18 high-priority countries for TB control that bear 85% of the TB burden and 99% of the MDR-TB burden. The study aimed to characterize Mycobacterium tuberculosis isolates obtained at different time points in Estonia to assess trends in evolution of drug resistant TB.

**Design/Methods:** The collection included 278 M. tuberculosis isolates obtained in 1999 and 2014-2015. They were subjected to drug susceptibility testing, genotyping, analysis of drug resistance mutations and genotype-specific markers.

**Results:** The Beijing genotype was the most prevalent and increased from 28.6% in 1999 to 38.5% in 2015. The non-Beijing strains represented Latin-American Mediterranean (LAM), Ural, Haarlem and T families. Drug resistance showed an increasing proportion of isolates resistant to two and more drugs from 21.7% to 29.1%, while the all isolates of the Beijing B0/W148-cluster

(“successful Russian strain”) were MDR or pre-XDR. The pre-XDR status remained limited to the Beijing genotype and did not emerge among other genotypes. In contrast, the drug resistance rate decreased in LAM isolates and remained stable and moderate in the Ural isolates. An increased level of monoresistance among some of the non-Beijing genotypes highlights possible non-compliance or inadequate treatment.

**Conclusions:** The analysis of the *M. tuberculosis* collections in Estonia revealed the increasing prevalence of the MDR/pre-XDR Beijing B0/W148-cluster. At the same time, the drug resistance level remained low in other, non-Beijing genotypes and their diversity increased. Taken together, these findings may be interpreted as evidence of (i) success of the national TB control program against non-Beijing genotypes (reduced clustering, no dissemination of particular types), but (ii) lack of success against the most hazardous, MDR and hypervirulent variant of the Beijing genotype.

**Acknowledgement.** Russian Science Foundation (grant 19-14-00013).

### OA-31-692-23 Comparing the epidemiology and clinical characteristics of childhood tuberculosis through active and passive case finding

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**Background:** Childhood tuberculosis can be found via passive case finding (PCF), diagnosing a symptomatic child, and active case finding (ACF), discovering a child through contact tracing. Most high prevalence areas perform PCF, but as ACF is introduced, the clinical and radiologic findings may differ. We compare clinical, radiographic, microbiologic and epidemiological characteristics of children diagnosed through ACF and PCF.

**Design/Methods:** A retrospective cohort study of all patients diagnosed with TB from 01/01/2012-12/31/2019 at Texas Children’s Hospital. ACF is TB in a child who had not previously sought care before identified via contact tracing, immigration screening, or screening for incarceration. Severity of disease was based on location of illness, imaging and bacteriology/histopathology. Associations between PCF/ACF and demographics, disease severity, and microbiology were analyzed.

**Results:** Of 178 patients, 80 (45%) were diagnosed via ACF. ACF patients were more likely to be US-born (OR: 2.29, [95% Confidence interval (CI): 1.12-4.67]) and younger (mean 6.18 vs 8.84 years,  $p=0.016$ ). Only 2.5% of ACF patients had extrapulmonary disease, compared to 45% of the PCF group ( $p<0.0001$ ). All 14 severe extrathoracic cases were in the PCF group (10 central nervous system disease, 3 ocular disease, and 1 spondylitis). Fewer patients in the ACF group had severe intrathoracic findings (11% vs 39%,  $p<0.001$ ): miliary disease

(0% vs 10%,  $p=0.006$ ), cavity (1% vs 9%,  $p=0.04$ ), and multilobar involvement (7.5% vs 22.4%,  $p=0.006$ ). ACF patients had more hilar/mediastinal adenopathy (OR: 2.51, [CI: 1.34-3.72],  $p=0.004$ ). ACF patients were less often cultured (38% vs 89%,  $p<0.0001$ ) and had less microbiological confirmation by cultures or PCR (21% vs 52%,  $p<0.0001$ ).

**Background and challenges to implementation:** Childhood tuberculosis can be found via passive case finding (PCF), diagnosing a symptomatic child, and active case finding (ACF), discovering a child through contact tracing. Most high prevalence areas perform PCF, but as ACF is introduced, the clinical and radiologic findings may differ. We compare clinical, radiographic, microbiologic and epidemiological characteristics of children diagnosed through ACF and PCF.

**Intervention or response:** A retrospective cohort study of all patients diagnosed with TB from 01/01/2012-12/31/2019 at Texas Children’s Hospital. ACF is TB in a child who had not previously sought care before identified via contact tracing, immigration screening, or screening for incarceration. Severity of disease was based on location of illness, imaging and bacteriology/histopathology. Associations between PCF/ACF and demographics, disease severity, and microbiology were analyzed.

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**Conclusions:** Patients in the ACF group were younger, had less severe clinical manifestations, and had almost no extrathoracic disease. Clinicians need to be aware that the common clinical and radiographic presentations in children differ between PCF and ACF.

### OA-31-693-23 Increasing tuberculosis incidence rates and inequitable treatment outcomes for young people with tuberculosis in Brazil: a national retrospective cohort study

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**Background:** Young people are a neglected population in tuberculosis elimination efforts, and are vulnerable to the effects of social and economic deprivation. Unlike children, young people are likely to contribute to onward transmission of tuberculosis, further perpetuating the epidemic.

**Design/Methods:** We conducted a national retrospective cohort study using Brazilian tuberculosis registry data. We included persons between 10 and 24 years, newly diagnosed with tuberculosis between 1st January 2015 to 31st December 2018. Unfavourable outcomes were defined as loss to follow-up, development of drug-resistant tuberculosis, treatment failure, change in treatment regimen or death. Favourable outcomes were defined as treatment completion and cure. We estimated the association between the characteristics of young people and treatment outcomes through complete case and sensitivity analyses.

**Results:** We included 42 291 young people newly diagnosed with tuberculosis in Brazil with recorded treatment outcomes. Most were male (65%), in young adulthood (62%), identifying with black or brown skin colour (65%) and urbanites (89%). Furthermore, 16% were deprived of liberty and 53% had lower educational attainment than expected for their age. TB incidence rates for young adults ranged from 48/100 000 to 58/100 000, between 2015 and 2018. Young people who were homeless (ORadj 2.58; 95% CI: 1.64-4.07), AIDS/HIV-positive (ORadj 2.93; 95% CI: 2.37-3.61), using illicit drugs (ORadj 2.20; 95% CI: 1.84-2.62) or who had lower educational attainment than expected (ORadj 1.61; 95% CI: 1.42-1.82) were most likely to experience unfavourable treatment outcomes. Despite the vulnerabilities of young people with tuberculosis, treatment supervision (52%) and receipt of governmental cash transfers (10%) were limited.

**Conclusions:** The individual, social and health vulnerabilities of young people with tuberculosis are extensive and complex. Young people warrant further recognition in TB elimination efforts in Brazil, and beyond, with recognition that young people represent the health and prosperity of tomorrow.

## E-POSTER SESSION (EP)

### EP20 Community healthcare workers in evidence

#### EP20-288-23 Household contact tracing of pulmonary bacteriologically confirmed tuberculosis patients by community health workers in Bumula Sub County

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**Background and challenges to implementation:** The World Health Organization (WHO) recommends for contact tracing among household of bacteriologically Tuberculosis (TB) patients. This recommendation has not been fully implemented in many countries due to system barriers like limited health workforce.

In Bumula sub county contact invitation is conducted by health care workers where TB patients are encouraged to bring all contacts for screening though most of the contact never turns up. The AMREF project sought to determine whether community health workers (CHW) can effectively implement contact tracing.

**Intervention or response:** From January 2019 through December 2019, CHW in ten health facilities in Bumula Sub County were trained on how to conduct TB contact tracing. Household contacts of index TB cases were physically tracked in their homes by CHW and screened using the standard WHO intensified case finding tool. Sputum was collected from presumptive TB contacts and referred for microscopic or GeneXpert examination. Identified TB cases were initiated on TB treatment. Children below 5 years were referred to the health facility those with TB were initiated on treatment and those with no TB were initiated on Isoniazid preventive therapy (IPT).

**Results/Impact:** During the study period, 743 contacts of 69 index sputum-positive TB cases were tracked and screened of whom 56 were children below five years, of the children 2/56 (3.6%) were started on TB treatment and 54/56 (96.5%) on IPT. Of the adults identified 238/687 (34.6%) were presumptive cases out of whom 214/238(89.9%) provided sputum for testing; yielding 19/214(8.9%) sputum-positive and were initiated on TB treatment. This led to an overall 20% increase in the case notification rate and 70% increase in IPT uptake in children below 5 years.

**Conclusions:** Community health workers can effectively implement household contact tracing in resource limited settings. Contact tracing of bacteriologically TB patient can be used as a strategy in finding of the missing TB cases.

#### EP20-289-23 "After we gave their children Polio vaccine we also asked if anyone was coughing...". Exploring program integration through experiences of frontline health workers in Nigeria

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**Background:** In July of 2019, a novel intervention of integrating community TB case finding into periodic polio vaccination campaigns was implemented in Anambra and Kaduna states of Nigeria. Essentially, lay health workers, who carry out house-to-house vaccination were empowered to conduct TB clinical screening in households and in some cases, collect sputum samples. This qualitative research aimed to learn from their experiences to help plan for sustainable integration.

**Design/Methods:** Lay health workers (LHWs) who participated in the integration of household TB screening during the polio vaccination exercise were selected for this study. Five to six LHWs were purposively selected from each of the three senatorial zones in each state. In-depth interviews, conceived from an interpretivist epistemological standpoint were conducted for 32 LHWs across the two states. The audio recordings were transcribed using a naturalised approach. Subsequently, transcripts were coded in segments before the application of thematic analysis on the data.

**Results:** The majority of interviewed LHWs identified presumptive (30/32) or confirmed TB cases (18/32). About one third (12/32) had over 10 years' experience in polio vaccination campaigns while eight were solely community TB workers.

Some key themes that emerged from the data include a high level of acceptance of the intervention by the community, the reduced stigma associated with TB interventions, simplicity of the intervention, and the important role of culturally sensitive approaches. The community TB workers who participated in this intervention reported greater community acceptance to TB screening in households and less stigma towards them compared to their previous community TB work. LHWs also shared TB information in all households visited.

**Conclusions:** This community TB case finding intervention was helped by the relatively simple actions (and documentation) that the LHWs were expected to perform. The experience and community acceptance of the Polio structure was leveraged to achieve community TB enlightenment and case finding.



## EP20-290-23 Can point-of-care CRP improve symptom-based TB screening for detection of TB in the community?

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**Background:** WHO recommends TB systematic screening in high-risk groups but current tools are limited to symptom-based screening, which has low sensitivity, and chest x-ray (CXR), which requires infrastructure and trained interpreters, often not routinely available in TB-endemic areas. C-Reactive Protein (CRP) has been suggested as a potential TB triage test though mostly in clinical settings. We aimed to assess the performance of a point-of-care (POC) CRP test for screening TB in the community in two high burden countries.

**Design/Methods:** We conducted a cross-sectional study in three communities in Zambia and one in South Africa, nested in a TB prevalence survey. Participants with symptoms suggestive of TB and/or computer-aided detection (CAD) for TB score  $\geq 40$  on their CXR submitted sputum samples for GeneXpert and TB culture. POC-CRP testing was performed in all participants submitting sputum. We calculated the sensitivity and specificity of POC-CRP, alone and combined with symptom-screening to detect TB, compared to culture.

### Results:

Screening	All				People living with HIV				
	Sensitivity <sup>a</sup>		Specificity <sup>b</sup>		Sensitivity <sup>a</sup>		Specificity <sup>b</sup>		
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Symptoms <sup>1</sup>	37.8 (14/37)	22.5-55.2	68.8 (457/664)	65.1-72.3	42.9 (6/14)	17.7-71.1	68.4 (93/136)	59.9-76.1	
CXR <sup>2</sup>	94.6 (35/37)	81.8-99.3	21.4 (142/664)	18.3-24.7	92.9 (13/14)	66.1-99.8	20.6 (28/136)	14.1-28.4	
POC-CRP <sup>3</sup>	$\geq 10$ mg/dl	43.2 (16/37)	27.1-60.5	85.1 (565/664)	82.2-87.7	42.9 (6/14)	17.7-71.1	78.7 (107/136)	70.8-85.2
	$\geq 5$ mg/dl	56.8 (21/37)	39.5-72.9	70.5 (468/664)	66.9-73.9	64.3 (9/14)	35.1-87.2	63.2 (86/136)	54.5-71.3
Symptoms <sup>1</sup> or POC-CRP	$\geq 10$ mg/dl	56.8 (21/37)	39.5-72.9	58.4 (388/664)	54.6-62.2	71.4 (10/14)	41.9-91.6	55.9 (76/136)	47.1-64.4
	$\geq 5$ mg/dl	67.6 (25/37)	50.2-82.0	49.7 (330/664)	45.8-53.6	85.7 (12/14)	57.2-98.2	46.3 (63/136)	37.7-55.1

<sup>1</sup> Cough  $\geq 2$  weeks OR cough with 2 or more of: fever  $\geq 2$  week or chest pain  $\geq 2$  weeks or night sweats  $\geq 2$  weeks or unexpected weight loss last 1m <sup>2</sup> Chest X-ray with CAD score  $\geq 40$  <sup>3</sup> Point-of-Care C-Reactive Protein <sup>4</sup> Culture positive results=37 <sup>5</sup> Culture negative results=664 <sup>6</sup> Culture positive results=14 <sup>7</sup> Culture negative results=136

[Table 1. Sensitivity and specificity of symptom, CXR and CRP-POC screening, and of the combination of CRP-POC with symptoms]

701 participants were enrolled in the study, 37 had culture confirmed TB. The sensitivity of POC-CRP alone was 43% (16/37) and 57% (21/37), and specificity of 85% (565/664) and 71% (468/664) when using cut-offs for CRP of  $\geq 10$ mg/dl and  $\geq 5$ mg/dl, respectively. Symptom screening alone had a sensitivity of 38% (95% CI 22.5-55.2) and a specificity of 69% (95% CI 65.1-72.3). The combination of POC-CRP with symptom-screening improved sensitivity to 57% (95% CI 39.5-72.9) for a CRP cut-off of  $\geq 10$ mg/dl and 68% (95% CI 50.2-82.0) for a CRP cut-off of  $\geq 5$ mg/dl. In people living with HIV the sensitivity of POC-CRP combined with symptom-screening increased to 71% (95% CI 41.9-91.6) and 86% (95% CI 57.2-98.2) and for CRP cut-offs of  $\geq 10$ mg/dl and  $\geq 5$ mg/dl, respectively.

**Conclusions:** POC-CRP combined with symptom-screening, can be a potentially useful to identify TB cases in the community in high-burden countries, where other recommended tools, such as CXR might be of limited availability.

## EP20-291-23 Finding the missing tuberculosis cases in Niger state, Nigeria through targeted community outreaches and sensitization of primary health facilities

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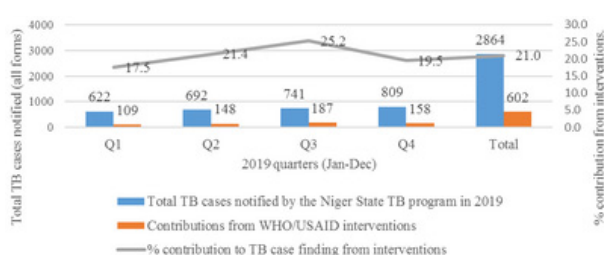
**Background and challenges to implementation:** With an estimated 331,000 missing TB cases in 2018, Nigeria accounts for 9% of missing TB cases globally. Niger state accounts for nearly 4% of Nigeria's missed cases, with an estimated treatment coverage of 16.5%. To address this gap, the World Health Organization, funded by United States Agency for International Development introduced targeted community outreach and stimulation of non-TB reporting health facilities in Niger state.

**Intervention or response:** Using population density, proximity to a health facility, HIV/TB burden and TB treatment coverage, (6) Local Government Areas (LGAs) were selected in Niger State. For each LGA, TB supervisor (1), laboratory technicians (2), and community mobilizers (4) were trained on how to identify presumptive TB cases, sputum collection and linkage of confirmed TB cases to nearest health facilities for TB treatment. Sputum cups and stipend were provided to TB supervisors to facilitate sputum transportation from hard to



reach areas. Also, TB supervisors were trained on identifying, engaging and sensitizing primary healthcare (PHC) facilities staff in their LGAs not providing any form of TB services to their patients, and refer presumptives TB cases for diagnosis and treatment

**Results/Impact:** Between January to December 2019, targeted community outreach was conducted in 52 rural villages (Mokwa-19, Agaie 12, Kotangora-10, Chanchaga-7, Bida-2 and Katcha-2). Additional 244 (M:144; F:130) all forms of TB cases were notified and 3,704 (M:1689; F:2015) presumptive TB cases were identified from community outreaches and 358 (M:195; F:163) TB cases were notified from 250 PHC facilities. The graph below shows trends of quarterly contributions to TB case finding from interventions.



[Figure.]

**Conclusions:** Multi-pronged approach involving both community and facility-based interventions successfully identified additional TB cases in Niger State. National programme to scale-up approaches in order to address the challenge of missing TB cases in Nigeria.

### EP20-292-23 The roles of community cadres to apply the virtual case finding due pandemic COVID-19

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**Background and challenges to implementation:** Tuberculosis (TB) remains a high burden disease in many countries including Indonesia. In 2018, Indonesia was expected to have a case load of 845,000, but it only notified 563,879 or almost 30% of the total expected cases missing. Lembaga Kesehatan Nahdlatul Ulama (LKNU), a faith-based organization, manages a community TB program in 61 districts which focus on TB active case finding through contact investigation. The trained community cadres carry out home visits to screen household and close contacts of the TB index cases.

**Intervention or response:** The COVID-19 lock-down has forced LKNU to stop door to door activities. To overcome this challenge, LKNU is implementing an innovative way to use mobile phones as part of virtual screening.

**Results/Impact:** This abstract based on reviewing regular weekly district report analysis. Currently, 797 out of 6,051 community cadres are carrying out the virtual screening, with 7,559 people screened within two weeks after starting activities. 437 TB symptomatic were referred to community health centers, 10 showed up for testing and 3 of whom were TB positive.

The mobile phone access as well as ability to use the devices remain barriers for scaling up this approach. A similar challenge exists on the community side since not all contacts have access to phones. Also, many referred symptomatic have access issues for testing since community centers do not provide sputum testing services because of COVID-19. But on the contrary, there are community members feel comfortable with this mechanism because privacy issue.

**Conclusions:** The virtual screening can be an alternative for case finding, especially during the pandemic. An intensive observation must be made and continue to modify the approach to be more effective. The community cadre' knowledge on the new mechanism must be improved and health facilities which do not provide TB testing services must provide information for accessible alternatives.

### EP20-293-23 Finding missing people with tuberculosis: the role of community health workers/volunteers in TB contact tracing/investigation in Tanzania (January –March 2020)

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**Background and challenges to implementation:** Tanzania is among the 30 high burden countries with TB in the world. According to 2018 WHO report, Tanzania in 2017 missed 56% cases of TB from the estimated 154,000 cases, only 44% (68,500) were detected by the program, with treatment success of 90% percent. Despite the achievement in incidence decline, the country remains to be among 13 countries accounting for 75% of missed TB cases globally. Most smear or gene xpert positive TB patient's contacts are not traced and brought to care due to few or lack of follow up by overwhelmed health facility care workers from the facility.

**Intervention or response:** Amref health Africa in Tanzania is implementing community TB in eight regions through global fund in finding missing people with TB. The project uses community health workers/volunteers

(CHW/Vs) and TB expert patients in the community for the sensitizations and referral of the presumptive individuals to the health facilities. The project assigned the CHW/Vs to all the diagnosed TB patients registered at the health facility for the follow up at the community level between. Each CHW/Vs were given the number of TB patient contacts for tracing each week. The CHW/Vs were remunerated for the work with a monthly stipend and pay for performance approach for the number of presumptive cases referred or sputum collected.

**Results/Impact:** About 1,358 CHW/Vs were assigned 7,369 TB cases to do contact tracing in project regions. A total of 112,629 presumptive cases were found and 2,683 were diagnosed with TB and all started on the TB management. Additionally, Contact tracing for 32 MDR cases was conducted, 147 contacts were traced; 6 TB cases were diagnosed.

Periods	Index TB patient for contact tracing	Contacts Presumptive TB cases	Confirmed TB Patients	% Confirmed/ Index TB patients	% Confirmed TB/ Presumptive contacts
January	2,493	37,951	903	36%	2.4%
February	2,504	35,502	1,099	44%	3%
March	2,372	39,176	681	29%	1.7%
Total	7,369	112,629	2,683	36%	2.4%

*[Contact tracing among confirmed Index TB patients (drug sensitive) in project regions Jan - Mar 2020]*

**Conclusions:** Using CHWs-volunteers in contact tracing is of paramount importance in fastening the finding missing people with TB in the community.

### EP20-294-23 Community health workers at the frontline: task-shifting shows high TB sputum rates at primary health care level in King Cetshwayo District, KwaZulu-Natal, South Africa

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**Background and challenges to implementation:** In 2016, South Africa adopted the TB 90-90-90 targets: screening 90% of high-risk populations for TB, diagnosing and treating 90% of those with TB disease, and achieving 90% DS-TB treatment success rates by December 2020. These targets aim at reducing both TB incidence and

TB mortality. NGO Médecins Sans Frontières (MSF) in collaboration with National Department of Health (NDOH) set up strategies to close the gaps along the TB care cascade.

**Intervention or response:** In October 2019, MSF trained community health workers (CHW) started conducting high quality TB screening at first point of entry for all presenting to primary health care (PHC) facilities. Alongside identifying presumptive cases, CHW collect sputum samples and refer to clinicians if further investigations are required. Allocation of CHWs happened according to the facility's volume and with on-site agreement to adapt patient flow. DOH/MSF data collection tools are used to monitor activities. CHWs receive on-site supervision and monthly feedback.

**Results/Impact:** Screening rates vary between facilities, with on average 73% of patients being screened for TB. The yield of presumptive TB cases amongst all screened is 4%. Of all presumptive cases, sputum collection rates reached 91.1%. Alternative diagnostic tools such as clinical examination, chest X-ray and TB LAM are used in 8.9%. 5.9% of all presumptive cases are initiated on TB treatment.

**Conclusions:** Task-shifting TB screening and sputum collection to trained and well supported CHWs results in over 90% of all presumptive patients submitting sputa at PHC level. Regular feedback to fieldworkers rectifies gaps timeously. The yield of presumptive TB cases is lower than the expected 10% where TB burden is high, possibly due to using the traditional four-question screening-tool in a high HIV prevalent setting. Further training on atypical presentations of TB and upscaling of alternative diagnostic tools is recommended to find additional TB cases and reduce the TB burden.

### EP20-295-23 The comparative yield of contact investigations from an index patient-led contact tracing approach and a community health care provider-led approach

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**Background and challenges to implementation:** To prevent community TB transmission, WHO recommends active contact investigation among close contacts of infectious index TB cases to find missed TB cases early. Routinely collected data indicate that the yield from contact investigation in Uganda stagnated at 20%, far below WHO expected yield of 40%-80%. A community health care provider-led approach using trained lay community health care workers is the most used approach in Uganda where TB stigma in the community is very high and many youths are missed. Conventionally, a community health-worker visits an index's residence, screens contacts, collects a sample for testing and re-

turn test result. Positive cases are counselled and started on TB treatment. The Joint Clinical Research Center (JCRC) explored to determine the yield of contact tracing using an index patient-led approach.

**Intervention or response:** Selected index patients were oriented about TB transmission, common signs and symptoms of TB and how to prioritize close contacts. The value of screening family members, neighbors, social networks and the catastrophic costs of delayed TB diagnosis in case one had TB was explained. Majority of the index patients were males; youth 15-24 years and HIV negative. The index actively screened his close contacts and linked them to JCRC for further systematic TB screening and Xpert testing. Positive cases were counselled and started on TB treatment. Negative cases were started on TB preventive therapy. Details were recorded in the contact tracing register. This was conducted in three months with support from USAID Defeat TB.

**Results/Impact:** The yield of TB cases from Index patient -led contact tracing in three months was 80%, fourfold higher than 20% yield from conventional community health care provider -led approach.

**Conclusions:** Index patient -led contact tracing approach is an effective approach for finding missed TB cases quickly and could be employed among youths and communities with high stigma index.

### EP20-296-23 Improving systematic tb case finding for community platforms, in low-resource settings in Lao PDR

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**Background and challenges to implementation:** From 2010 to 2018, the National Tuberculosis Center (NTC) in Lao PDR increased its treatment coverage rate from 29% to 57%, driven by passive case finding, increased upfront GeneXpert testing and active case finding. However, TB cases continue to be missed from the primary health and community levels.

**Intervention or response:** The NTC implemented a comprehensive TB case finding model in two districts in Champasack province. Activities included: 1)introducing standard operating protocols (SOPs) for systematic TB screening at facilities, 2)engaging village health volunteers on TB screening and sample collection, 3) monthly data reporting and supervision to sites; 4)optimizing sputum transportation from facilities and vil-

lages and transitioning to 100% upfront GeneXpert testing; and 5)conducting active case finding based on high risk group mapping. Patient and costing data was collected on a monthly basis and analyzed and mapped using Tableau and MS Excel.



[Figure.]

**Results/Impact:** Trainings and monthly supervision were conducted for all 26 facilities in the two districts, covering 393 health workers. From the pre-intervention (January to June 2018) to intervention (January to June 2019) periods, TB case notification increased by 55% (124 to 192 TB cases). The TB symptomatics identified increased from 376 to 1,500 (~300%) and the number of presumptives tested upfront on GeneXpert increased from 369 to 1,179 (220%). Notably, village health volunteers identified 40% of the TB presumptives and 15% of TB cases. The pilot cost per case was \$312. The intervention was subsequently scaled up to all 10 districts of the province.

**Conclusions:** This pilot demonstrated the effectiveness of a scalable model to strengthen systematic TB case finding at facilities and at the community level using village health volunteers and active case finding drives. Based on the successes of this pilot, the NTC expanded the scope of the proven activities for its National Strategic Plan 2021-2025 and scaled this model to additional districts.

## EP21 TB as an occupational hazard

### EP21-297-23 Comparison of latent tuberculosis infections among general versus tuberculosis health care workers in Myanmar

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**Background:** Health care workers in high tuberculosis (TB) prevalence countries have to care for many cases thus increasing their risk of infection. The objective of the study was to compare the prevalence of latent TB infection between general health care workers and TB health care workers and also explore the associated factors.

**Design/Methods:** A cross-sectional study was conducted in Nay Pyi Taw, Myanmar from September 2019 to January 2020. Staff working at two general hospitals were recruited. Those allocated for TB care were classified as TB health care workers while the remaining were classified as general health care workers. Participants were interviewed using a structured questionnaire and screened for latent TB infection using a tuberculin skin test. Individuals who had an induration of 10mm or more with normal chest radiograph were regarded as having latent TB infection.

**Results:** The prevalence of latent TB infection among general health care workers was 2.04 times higher than that of TB health care workers (31.2% vs. 15.3%,  $p < 0.001$ ). Associated factors for latent TB infection included low education level (AOR: 1.96, 95% CI: 1.15 – 3.34), duration of work experience  $\geq 10$  years (AOR: 3.50, 95% CI: 2.13 – 5.74), a low knowledge of regular TB screening (AOR: 0.25, 95% CI: 0.13 – 0.47), and teaching cough etiquette to people with TB (AOR: 7.41, 95% CI: 2.59 – 21.23).

**Conclusions:** General health care workers are at higher risk for latent TB infection than TB health care workers indicating that there is a need to improve TB prevention within the general patient care context.

### EP21-298-23 Assessing TB case notification among coal miners and their contacts in Balochistan, Pakistan

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**Background:** Pakistan accounts for 6% of the global tuberculosis (TB) burden with an incidence rate of 265 per 100 000. Coal mining is a large industry in Pakistan, particularly in Balochistan. Previous studies have shown that TB is an adverse health effect for coal miners. In 2017, the case notification rate in Balochistan was 18 per 100 000. This TB REACH Wave 6 project implemented an active case finding intervention (ACF) to increase case finding of TB among the coal miners and their contacts.

**Design/Methods:** The project targeted five districts in Balochistan between January and December 2019. Three methods were adopted for ACF:

- 1) outreach camps,
- 2) verbal screening camps and;
- 3) household contact tracing of microbiologically confirmed (Bac+) patients.

Coal miners were screened through outreach camps and verbal screening by staff and camp screeners respectively. Once identified as Bac+ by GeneXpert, household contact screening was conducted by counsellors. All Bac+ cases were referred for treatment at DOTs centres. Data was collected on paper-based forms, digitized and analysed on EpiData version 3.1.

**Results:** During implementation, 10 999 persons were screened; 6 649 coal miners and 4 276 contacts. A total of 1 898 were identified as presumptive where 24 were Bac+ and put on treatment. Six patients are cured, eight are on treatment and two were lost to follow up.

**Background and challenges to implementation:** Active case finding interventions are recommended for miners, yet most focused on gold mining in Southern Africa. Coal miners are exposed to coal and crystalline silica dust and only a few studies exist in high burden countries on TB amongst them. Balochistan, Pakistan houses around 70,000 coalminers yet only notified 18 TB cases per 100,000 population in 2017.

**Intervention or response:** This project was implemented in five major coalmining districts of Balochistan province, hosting 80% of the coal miners, between January and December 2019 using three ACF strategies:

- 1) verbal screening camps

2) screening through outreach, and;  
3) household contact tracing of confirmed (Bac+) patients, which were placed on treatment in nearby facilities.

**Results/Impact:** During the study, 10,986 individuals were screened of whom, 1,896 (17.3%) were identified as presumptives, of which 24 Bac+ TB were identified (0.2 % of those screened). Twenty patients (83.3%) were cured, two (8.3%) lost to follow up, and two (8.3%) were transferred out, as depicted in table 1 below. The case detection was comparable to TB incidence in general population. Most cases (70%) were identified in a very early stage of disease through GeneXpert testing. This intervention drew attention to the sad plight of coal miners and the dearth of healthcare services for them leading to mitigatory measures.

Indicators	Intervention 1		Intervention 2		Intervention 3	Total
	Screening of coal miners through verbal screening chest camps	Screening of coal miners' families and associated mining communities through verbal screening chest camps	Screening of coal miners through community outreach	Screening of coal miners' families and associated mining communities through community outreach	Contact tracing of the Index TB cases	
Number of people screened	5,731	2,771	918	1505	61	10,986
Number of people with presumptive TB	1,052	429	151	246	18	1,896
Number of people with Bac+ TB	13	6	0	4	1	24
Number of Bac+ TB patients started on treatment	12	5	0	4	1	22
Number of Bac+ TB patients successfully treated	11	5	0	3	1	20

[Table 1. Screening and treatment outcome results of coal miners and their contacts in Balochistan, Pakistan]

**Conclusions:** We documented the first TB case finding intervention among coal miners, although unlike African gold miners, no visible surge of TB was found in Balochistan, nevertheless there was a tangible increase in case detection in the targeted districts due to mass awareness. Reports also indicate that the majority of coalminers upon falling ill mostly (90%) return home in Khyber Pakhtunkhwa province. To conclusively understand the TB burden in this marginalised population segment in Pakistan, further research is therefore required in the other provinces of Khyber Pakhtunkhwa, Punjab and Sindh as well.

## EP21-299-23 Reaching the feared but marginalised artisanal small-scale miners (ASM) community with tuberculosis (TB) services

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**Background and challenges to implementation:** The marginalisation of ASM in Zimbabwe originates from harassments, beatings and arrests from the law enforcing agents. In a desperate way to protect their interests, the illegal ASM have armed themselves with machetes. This has degenerated into the formation of rival gangs amongst themselves. The gangs have not confined themselves to the mining sites but have gone out into the surrounding communities indiscriminately unleashing machete attacks on innocent community members. This has made the ASM to be feared not only by the community but by the law enforcement agencies and outreach health service providers.

**Intervention or response:** Jointed Hands Welfare Organisation (JHWO) being a CSO rooted in the community, advocating against harmful norms under a Global Fund regional grant where ACHAP is an SR called TB in the mining sector (TIMS). The program intervention is in the hotspots district of Kadoma and Kwekwe. Implementing the community screening, community mobilisation and advocacy and the gender and human rights modules. The screening intervention is deliberately focused on feared ASM though ex-miners, family members of current and ex-miners benefit.

**Results/Impact:** A total of 11758 screenings have been conducted giving a yield of 2070 presumptive cases of which more than 50% have accessed diagnostic services with 100 % (n=20) accessing treatment support. Of which 100% of contacts have been traced and linked to services. 15 078 feared ASM has been reached on risk communication. A total of 34 gender and human rights report have been raised and addressed.

**Conclusions:** The feared marginalised ASM and their close family members have accessed their right to health services through the TIMS intervention. The intervention concludes that, while more can be done to reduce vulnerabilities in the feared ASM and associated challenges thereto, an impact of the intervention manifest in both the lives of the feared ASM, their families and the HIMS data.

## EP21-300-23 Evaluating the impact of tuberculosis infection prevention and control measures in key population wards in South Africa

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**Background and challenges to implementation:** Identifying people with tuberculosis (TB) in the community remains a priority for reducing the spread of TB and for ending TB in South Africa. As part of a strategy to “find the missing cases” in the country, the USIAD TB South Africa Project has collaborated with the National Department of Health to adopt an administrative control intervention named “Finding TB cases Actively and Separate Safely” (FAST) to address diagnostic and treatment delay. The strategy is implemented in 86 of 102 identified hospitals in the 11 districts supported the project to identify TB cases which would have been missed otherwise.

**Intervention or response:** We analyzed data from the National Health Laboratory Service to understand the impact of the FAST intervention on case finding in key population wards. For the purposes of this analysis, key population wards include occupational health services, antenatal care (ANC) and labor, pediatric and antiretroviral (ARV) wards in 2019.

**Results/Impact:** Table 1 describes cases identified in these wards. Compared to the pre-FAST period (n=15 facilities, 2017), we observed an overall increase in TB cases identified in key population wards. When taking number of facilities into account in both periods, using n=15 and n=86 for pre- and post-FAST, respectively, we also see increases in Occupational Health and ANC case finding (+90% and +77%, respectively). Even considering the increased number of facilities, we consider the overall percentage change (without respect to number of facilities) to be important, as these cases would have been missed otherwise in the additional 71 facilities added to the intervention. We attribute this improvement to improved administrative controls implemented universally in all wards of a hospital.

Ward	Cases (pre-FAST, 2017; n=15 facilities)	Cases (FAST, 2019; n=86 facilities)	% Change (absolute cases)
Medical	359	1344	73%
Occupational Health	1	58	98%
ARV	87	89	2%
Pediatric	20	81	75%
ANC/Labor	2	49	96%
<b>Grand Total</b>	<b>469</b>	<b>1621</b>	<b>71%</b>

[Table.]

**Conclusions:** The FAST strategy improves TB case identification, especially in wards which serve people in key populations in the TB epidemic (including people living with HIV, children, pregnant people and health care workers).

## EP21-301-23 Implementation of TB infection control practices: the case of Malawi

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**Background and challenges to implementation:** Tuberculosis infection prevention and control (TB IPC) is part of the key public health strategies to reduce the impact of TB among people living with HIV. The implementation of the TB IPC activities require a commitment of different units and staffs within a health care setting. By 2015, less than 25% of TB registration facilities were implementing recommended TB IPC practices in the country.

**Intervention or response:** In 2015, the national TB control programme developed TB IPC standard operating procedures (SoPs) and updated the national TB IPC guidelines. The SoPs and the new guidelines were distributed to health facilities throughout the country. About 850 health care workers from TB registration facilities were trained on the SoPs and new TB IPC guidelines. Regular mentorship and supportive supervision were conducted, with focus on TB IPC. The program procured and distributed personal protective equipment (N95 masks) to health facilities. Upper-room germicidal ultraviolet systems were installed in 30 district and central hospitals across the country. The program designated the monitoring mechanism to the implementation of TB IPC practices in the country. We therefore analyzed the implementation of TB IPC practices in Malawi from 2016 to 2019.

**Results/Impact:** By December 2019, out of 388 TB registration facilities in Malawi, 267(69%) facilities had functional TB IPC committees; from 19% in 2015. Personal protectives (N95 masks) were available in 91% of the TB registration sites from 55% in 2015. Percentage of facilities with TB IPC plans increased to 64% in 2019 from 21% in 2015. In more than 70% of the facilities, patients with a cough are identified, separated and fast-tracked for TB diagnosis.

**Conclusions:** There has been a great improvement in implementation of TB IPC practices in the country. The parameters used for assessment assist in measuring commitment of facilities to improve TB IPC practices in their respective facilities.

## EP21-302-23 Strengthening airborne infection control measures in Mumbai health facilities, 2016-2020

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**Background and challenges to implementation:** The COVID-19 pandemic highlights the importance of having infection control policy and practices in place at healthcare facilities (HCF) to protect patients and health care workers. SHARE INDIA and Centers for Disease Control and Prevention collaborated with Municipal Corporation of Greater Mumbai (MCGM) to build institutional capacity and strengthen airborne infection control (AIC) measures in primary and secondary HCF in ten municipal wards of Mumbai.

**Intervention or response:** MCGM's multi-disciplinary AIC unit (AICU) provided on-site AIC training, periodic monitoring assessments, and intensive follow-up and mentorship for each HCF. Baseline and four follow-up assessments were scheduled every ~4-6 months. A standardized 41-indicator monitoring tool reflecting national guidelines assessed AIC measures in 10 wards. Baseline assessments were phased during October 2016–February 2018 and follow-up assessments completed August 2019–Jan 2020.

**Results/Impact:** One hundred and forty-three HCF completed baseline and follow-up assessments over 29 months. Compliance with AIC policies and practices for administrative, environmental, and personal protective equipment measures increased over baseline by 16%, 4% and 22% respectively. Compliance with 'separation or triage of coughing patient', important for limiting transmission of respiratory pathogens, had the least improvement, from 1% to 10%. Overall, annual screening of healthcare workers for tuberculosis increased from 8% to 36%. The level of improvements of individual indicators varied: net difference in appointing a designated AIC point-person increased by 86%, masking coughing patients by 32%, implementing crowd management by 15%, ensuring open unobstructed windows by 12%, and correctly wearing N95 respirators by 22%.

**Conclusions:** Assuring effective AIC measures in HCF is essential to protect patients and health care workers but can be resource intensive and challenging to implement and monitor. An innovative model which included training, periodic assessments utilizing a standardized monitoring tool, and intensive follow-ups and mentorship by a dedicated AIC team was associated with improved compliance for all AIC measures.

Assessment indicators	Implemented (%) at baseline (Started in October 2016)	Implemented (%) at 1st follow up (March 2017)	Implemented (%) at 2nd follow up (Started in Sep 2017)	Implemented (%) at 3rd follow up (Started in May 2019)	Implemented (%) at 4th follow up (Started in Aug 2019)
Patient waiting areas not crowded (observed)	48%	51%	56%	59%	63%
Patients with cough are fast tracked to the health care provider (observed)	3%	26%	36%	51%	50%
Patients with cough are promptly separated from others (observed)	1%	6%	12%	13%	10%
Sputum is collected in a designated area far away from others, preferably outdoors (observed)	23%	68%	74%	65%	67%
All windows/doors opened without obstruction (observed)	68%	77%	80%	82%	80%
Staff wearing N-95 respirators correctly (observed)	31%	54%	59%	51%	53%
N-95 respirators are readily available to staff who have contact with coughing patients, patients with presumptive TB (observed)	54%	75%	75%	67%	70%
Staff are symptom screened for TB disease annually	8%	26%	26%	35%	36%

[Table. Changes in compliance with airborne infection control measures after AIC unit assessments at primary and secondary Mumbai healthcare facilities (n=143)]

## EP21-303-23 Screening of health care workers in Zambia: care of the carers 2018-2019

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**Background and challenges to implementation:** Health care workers (HCWs) are among the groups classified as high-risk populations for tuberculosis (TB) due to continuous exposure to individuals with undiagnosed and diagnosed TB at work. Although annual health screening is already a requirement for HCWs in Zambia, a country among the high TB and TB/HIV burden countries, there was no systematic enforcement of this requirement. In 2018, the National TB/ Leprosy Control Programme introduced the bi-annual TB screening of HCWs to provide care to the carers. HCWs with symptoms suggestive of TB may delay seeking health care for various reasons, such as stigma, inadequate confidentiality measures or incorrect perception of the risk. In this paper, we offered TB screening to HCWs to ensure early TB detection and reduce on TB related morbidity and mortality, hospitalization and help to retain a healthy workforce.



**Intervention or response:** Objectives: To determine the burden of TB among health care workers during the period 2018-2019

**Methodology:** Between 2018-2019, TB symptomatic screening was conducted on HCWs from health facilities in the ten (10) provinces in the country. HCWs with symptoms suggestive of TB were offered chest X-ray and asked to submit sputum for examination using Xpert/MTB/RIF test and smear microscopy. HCWs who participated in the screening included clinicians, nurses, laboratory staff, students, community healthcare workers, TB Treatment supporters, administrative staff and support staff such as cleaners and drivers.

**Results/Impact:** Of the 36,698 HCWs screened, 162 were diagnosed with TB during the period. Of the 162 HCWs diagnosed with TB, 159 (98%) and 3 (2%) were categorized as having susceptible TB and drug resistant TB respectively.

**Conclusions:** Zambia has not been conducting routine TB surveillance among HCWs. Early TB case detection and routine screening will be useful as a prevention strategy to help reduce nosocomial transmission in areas with both low and high TB incidence.

### EP21-304-23 Comparing two fit-test methods of commonly used N95 respirator in South African healthcare settings

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**Background:** The transmission of airborne infections such as Tuberculosis is a critical public health problem. While fit-testing of respirators is widespread, its implementation has been difficult, particularly in resource-constrained settings. This study aimed to compare fit-test results from the qualitative fit-test (QLFT) and quantitative fit-test (QNFT) methods with two N95-respirators, models 46827 and 46727, in resource-limited healthcare settings in South Africa.

**Design/Methods:** With the two fit-test methods used, QLFT relies on the user's ability to taste and/or smell the test agent, whereas the QNFT uses a porta-count to measure the amount of exposure to the user. This cross-sectional study was conducted at two district hospitals in Tshwane, South Africa. Ninety-nine HCWs were recruited through a non-probability, convenient sampling method and underwent sequential QLFT and QNFT fit-tests. To ascertain the degree of agreement between the two fit-tests, a Kappa (K) statistic was used.

**Results:** The degree of uncertainty estimated using the 95% confidence interval showed that HCWs were up to almost seven times more likely to pass a QLFT test than a corresponding QNFT. Furthermore, results indicated that the fit-test methods consistently disagreed (K=-

0.02). With respect to the effect of the N95-FFR model, an overlap in the confidence intervals indicated that there was no statistically significant difference in fit-test outcomes between the two N95-FFRs.

**Conclusions:** These results indicate that while fit-test results may differ between QLFT and QNFT, the type of respirator model may not influence outcomes. Due to its stringent nature, the QNFT emerged as the method of choice. Findings in this study set a standard against which future efforts in this field can be measured; they demonstrated the need for convenient but more efficient and reliable fit-test methodologies that could be applied in low to middle-income countries.

### EP21-305-23 Screening of latent tuberculosis infection in healthcare workers at a hospital in South Africa using interferon gamma release assay: Preliminary findings

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**Background:** In South Africa, healthcare workers (HCWs) are at a three to six-fold greater risk of acquiring tuberculosis (TB) disease than the general population. Surveillance for latent TB infection (LTBI) as well as disease is important to protect both the HCWs and patients to whom they provide healthcare.

Although current WHO guidelines recommend regular screening of HCWs in low incidence settings, the feasibility, implementation considerations and value in high incidence settings is incompletely understood. We performed a preliminary analysis to determine uptake and prevalence of LTBI active disease among the cohort of staff (both HCW and ancillary) at the Pretoria West District Hospital, Gauteng.

**Design/Methods:** Consenting individuals had TB symptom screening administered at baseline; demographic data, medical history and risk factors collected using a structured questionnaire. Blood for the QFT-Plus assay was drawn to test for LTBI. Patients will be monitored over the period, but we only report the baseline findings available.

**Results:** A total of 272 HCWs were tested by the QFT Plus assay for latent TB, 231 (85%) were female, 41 (15%) male and with the median age being 42 years across all

participants. Of these, 121 (44.5%) were LTBI positive and 129 (54.8%) negative. Two (0.7%) HCWs had and indeterminate QFT-Plus results. No association was observed between HIV status and IGRA positivity.

Previous TB Dx	Intermediate	Negative	Positive	TOTAL	% IGRA positive
No	2	143	109	254	42.9%
Yes	0	6	12	18	66.7%
TOTAL	2	149	121	272	44.5%
Household TB contact past year	Intermediate	Negative	Positive	TOTAL	% IGRA positive
Yes	0	8	8	16	50.0%
No	1	138	105	244	43.0%
N/A	1	3	8	12	66.7%
TOTAL	2	149	121	272	44.5%

[Table.]

**Conclusions:** Based on the preliminary results, the uptake and general interest from staff was good. The prevalence of LTBI in this setting is 44.5% in HCWs. Operationally, the test has very stringent time frames from sample collection to laboratory processing and required careful planning. Nonetheless, the test performance was good with minimal indeterminate rates. Follow up of the cohort to measure incidence rates of LTBI and active disease is planned as well as expansion to two geographically distant hospitals to assess feasibility in different setting.

### EP21-306-23 Yield of tuberculosis infection among health care workers in Afghanistan; a cross-sectional study

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**Background and challenges to implementation:** About one-third of the world's population may have latent tuberculosis infection (LTBI). Health care workers (HCW) are a high-risk category because of their professional exposure. The estimated TB incidence is 189 in 100,000 population and 10,000 Afghans die of TB every year. In 2019, over 450,000 presumptive TB patients attended/tested for TB in public health care facilities. NTP notified 52,770 all forms TB cases. These patients attend health care settings at least twice in a month. This poses extreme exposure of HCW to TB infection. The aim was to estimate the yield of TB infection and disease among HCWs.

**Intervention or response:** This cross-sectional assessment and we selected health facilities using a systematic sampling technique. Participants were interviewed about sociodemographic and exposure variables and received tuberculin skin tests (TST) for LTBI and for active disease using chest radiography. The TST was read in 48-72 hours. The X-ray was interpreted by radiologists. This assessment was funded through USAID funded TB project of Challenge TB.

**Results/Impact:** In total, 4,648 HCW were approached to participate in the assessment. Of them, for 3,686 TST administered. The yield of LTBI was found to be 47.2% (1,738 workers). Multivariate analysis showed that a body mass index of  $\geq 30$  and marriage were associated with an increased risk of LTBI. Underweight (body mass index of  $\leq 18$  and below) and normal body mass index had no association with increased risk of LTBI. Also, 26 HCW had active TB disease. The yield of TB disease was 705 in 100,000 population that is four times higher than estimated incidence for Afghanistan (189/100,000).

**Conclusions:** Conclusion: The yield of LTBI and active TB disease are high among health care workers in Afghanistan. We recommend instituting infection control measures in health facilities and screening workers for timely TB diagnosis.

### EP22 TB adherence to treatment

#### EP22-307-23 Implementation of Tuberculosis Preventive Treatment (TPT) in South Africa: the urgent need to address gaps

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**Background and challenges to implementation:** Tuberculosis (TB) and HIV are major global public health concerns. In South Africa (SA), TB remains the leading cause of mortality among people living with HIV (PLHIV), and studies have shown that TB accelerates HIV disease progression. Providing tuberculosis preventive treatment (TPT) to people at risk of progressing to TB disease; decreases TB transmission and TB-related mortality. The SA guideline stipulates a 12-month course of TPT for PLHIV on antiretroviral therapy (ART).

We sought to analyze TPT implementation in 27 South African districts supported through the US President’s Emergency Plan for AIDS Relief (PEPFAR).

**Intervention or response:** We used descriptive statistics to compare TPT initiations and completions between fiscal year (FY) 2018 (October 1, 2017 to September 30, 2018) and FY 2019 (October 1, 2018 to September 30, 2019) through data reported in PEPFAR’s Data for Accountability, Transparency and Impact Monitoring (DA-TIM).

**Results/Impact:** Among 238,471 PLHIV initiated TPT in FY 2018, 123,554 (52%) were new on ART. Of those initiated on TPT, 111,772 (47%) completed at least six months and marked a 9% increase from FY 2017. In FY 2019, 351,049 PLHIV initiated TPT, 164,485 (47%) of whom were new on ART. Of those initiated on TPT, 193,536 (55%) completed therapy, which is a slight improvement from FY 2018.

**Conclusions:** Although TPT initiations improved, completions remained low. South Africa’s large scale TPT implementation is challenged by weak health systems, including supply chain interruptions resulting in poor adherence to TPT. Implementing strategies to prevent TB transmission and progression to active disease in PLHIV remains a priority. In 2020, SA is scaling up short course Isoniazid-Rifapentine (3HP) as a potential game-changer to prevention of TB among PLHIV. PEPFAR continues to work with the National Department of Health and its partners to catalyze scale-up of TPT initiations and completions across all 27 focus districts.

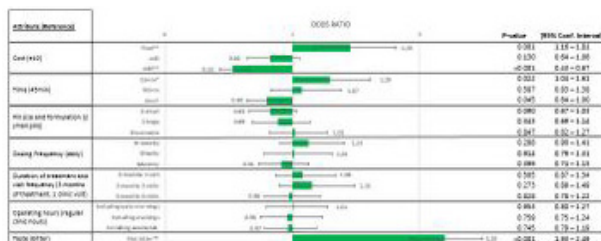
**EP22-308-23 Tuberculosis preventive treatment preferences among children in Eswatini: a mixed-methods study**

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**Background:** Tuberculosis preventive treatment (TPT) initiation and completion rates, using the standard six-month isoniazid course are suboptimal globally. Shorter TPT regimens have demonstrated safety and efficacy in children and may improve adherence but are not widely used in high TB-burden countries. Understanding preferences regarding TPT regimens’ characteristics and service delivery models is key to effectively implementing TPT.

**Design/Methods:** We conducted a mixed-methods study to examine TPT preferences among children 10-14 years in Eswatini, an African country with high TB-burden. We conducted 20 in-depth interviews in 2018 and enrolled 150 children in a discrete choice experiment (DCE) in 2019. Drug regimen and service delivery attributes in the DCE were pill size and formulation; dosing frequency; medication taste; duration of TPT and visit frequency; visit cost; clinic wait time; and clinic operating hours. We used an unlabeled, binary choice design for the DCE and fixed effects logistic regression modeling for analysis. Thematic analysis was used for the qualitative data analysis.

**Results:** In the DCE, median age was 12 years (IQR, 11-13), 49% female. Children were willing to make trade-offs, with medication taste, cost, and wait-time statistically significant characteristics driving preferences (Figure 1). Medication taste was most important. Children noted in qualitative interviews that better tasting pills are easier to swallow “...when pills are bitter we can’t take them; when they are nice... they are easy to take.” Some reported not taking or discarding bitter tasting pills. Long lines were discouraging, “...waiting for long, I get discouraged to come back...”.



\* <0.05, \*\* <0.01

[Figure 1. Results of discrete choice experiment in children]

**Conclusions:** Children indicated that medication taste is a more significant driver of choice than decreased duration or dosing frequency of TPT regimens. New TPT regimens that are adopted in Eswatini need to consider children’s preferences. More research is needed to better understand the extent to which their preferences drive initiation, treatment adherence and completion rates.

### EP22-309-23 Low completion rate of once-weekly rifapentine plus isoniazid regimen among elderly population

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**Background:** To conquer the challenge of aging, we'd like to clarify whether the uptake rate and interruption rate of two tuberculosis preventive therapy (TPT) regimens (the weekly rifapentine plus high dose isoniazid, 3HP and the 9-month isoniazid, 9H) among elderly population (aged 65 years and up) were improved by providing 3HP as an alternative choice to 9H, as it did among young population.

**Design/Methods:** Contacts with diagnosis of latent tuberculosis infection (LTBI) were enrolled during 2016-2018. Demographics, treatment uptake, regimens and treatment outcome were collected from the National TB Case Management System. All patients were observed until the date of event (developing TB), death, interruption of TPT treatment or the end of September, 2019. The analysis was stratified by regimens and calendar year.

**Results:** The overall uptake rates of TPT were 80%, 83% and 86% in 2016, 2017, 2018, respectively, but the rates amongst elderly population were 73%, 74% and 78% (test for trend,  $p=0.003$ ). The total population started TPT increased from 5082 in 2016 to 6935 in 2017 and stabilized at 6613 in 2018. Overall 3HP uptake proportions increased from 54% to 70% to 74%. However, the absolute number of those commencing treatment amongst the elderly increased from 1049 to 1436 to 1522 while 3HP uptake proportions increased from 39% to 39% to 58%. Nevertheless, the lower interruption rates of TPT for any reason amongst elderly were not in line with observations for those aged 65 years and below when comparing 3HP and 9H (table). Up to 18% of elderly patients had to interrupt LTBI treatment, irrespective of 3HP or 9H.

		Under 65 year-old			65 year-old and up		
		3HP	9H	P value	3HP	9H	P value
interruption for adverse events	2016	177(7.6%)	125(7.3%)	0.685	39(9.6%)	53(8.2%)	0.435
	2017	336(8.2%)	110(7.8%)	0.603	95(12.5%)	73(10.8%)	0.299
	2018	306(7.6%)	91(8.4%)	0.403	166(13.2%)	69(10.7%)	0.136
interruption for any reason	2016	306(13.2%)	288(16.8%)	0.001	60(14.8%)	100(15.5%)	0.754
	2017	522(12.8%)	233(16.5%)	<0.001	153(20.2%)	137(20.2%)	0.992
	2018	451(11.3%)	191(17.6%)	<0.001	161(18.4%)	133(20.6%)	0.269

[Table.]

**Conclusions:** Although shorter regimens can increase uptake rates of TPT, the interruption of 3HP treatment amongst the elderly did not make itself a better TPT solution for aging populations.

### EP22-311-23 Risk based patient centred strategies for TB treatment. Inference from a prospective cohort study

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**Background and challenges to implementation:** Tuberculosis (TB) still represents a major health problem in Latin America. From 1998 to 2018, treatment success and default rates ranged from 53-74% and 15-20% respectively in high burden areas. Implementation of treatment supervision is limited. Poor adherence represents a major threat for TB control and promotes emergence of drug resistance. To optimize strategies for prevention and management we need to adapt available resources and implement patient centered approaches. We evaluated the effect of different treatment strategies and socioeconomic support on treatment outcomes in patients at high and low risk of default based on published prediction models.

**Intervention or response:** Patients with first treatment of pulmonary TB were assigned to a low or high-risk group (median probability of default of 12%) according to baseline characteristics. Interventions were categorized in four groups based on the combination of self-administered vs. different degrees of supervision and being registered or not in a conditional cash transfer (CCT) program. We used propensity score and inverse probability weighting (IPW) to estimate treatment effects on TB outcomes adjusting for potential confounders.

**Results/Impact:** Treatment categories ranged from 1) self-administered treatment and no CCT, 2) only CCT, 3) only supervision and 4) both. High-risk patients (n 535) showed adjusted default rates of 35%, 15.5%, 11.7% and 7.4% and success rates of 54%, 75.8%, 74.3% and 90% respectively. Among low-risk patients (n 427), only those in category 4 showed significantly different rates compared to the other 3 (adjusted default rates of 11.3% vs. 3.6% and success rates 77.2% vs. 94.3% respectively ( $p<0.01$ )).

**Conclusions:** The protective effect was especially marked in the high-risk group and patients in category 4. The implementation of different treatment strategies considering a patient baseline risk, organization of health care and interventions for social inclusion will probably result in better TB outcomes in resource-constrained systems.

### EP22-312-23 Perspectives of MDR-TB patients on the use of treatment supporters: experience from Lagos, Nigeria

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**Background:** Globally, Nigeria is among the countries with the highest burden of MDR-TB. Treatment capacities for MDR-TB have been expanded to meet the demand created by this high burden with both domestic funding and developmental assistance for health. Both hospital and community-based models of care are available to patients to ensure that the gap between diagnosis and enrolment for care is closed. It is however critical that the quality of the available treatment services is optimal and that the services are delivered in a patient-centered approach.

**Design/Methods:** A qualitative study was conducted to explore the perspectives of MDR-TB patients on the use of treatment supporters and the quality of psychosocial support provided to them in the course of their treatment. An in-depth interview was conducted for 10 MDR-TB patients who were enrolled for care in Lagos, Nigeria.

**Results:** Patients expressed that the treatment supporters are very supportive. They explained that the treatment supporters educated them on the adverse effects of the medications in simple, layman's language and often, this improved their adherence to treatment. Many of the respondents interviewed said they preferred family members and close relatives as treatment supporters because they were more empathetic. One of the patients interviewed said "I would have died if not for my treatment supporter who ensured that I used my medications". Psychosocial, and physical, support from treatment supporters who were family members was also generally perceived to be better than that provided by non-family members.

**Conclusions:** The use of treatment supporters was found to be effective in ensuring treatment adherence among MDR-TB patients. From the patients' perspectives, family members were preferred as treatment supporters because of the closeness and the ability to support the patients physically and emotionally in the course of treatment.

### EP22-313-23 Improving treatment adherence with technology and patient-centered care in Morocco

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**Background and challenges to implementation:** In Morocco, the paper-based system and the shortage of TB (Tuberculosis)-related health workers indicate challenges in the management of tuberculosis patients in high-risk groups. In addition, the undifferentiated TB management that does not take into account for various patient situations has an effect on poor treatment adherence. We would like to describe an intervention that uses a patient-centered approach and mHealth (mobile health) technology for improving the treatment adherence.

**Intervention or response:** In a retrospective cohort study that resulted at the e-poster presentation in 2015 Union, the lost to follow-up rate was significantly lower in the mHealth-group. Based on this effectiveness of mHealth project, we have performed TB management to each patient based on various criteria such as demographic characteristics, socioeconomic status, areas (rural or urban), health literacy levels and distance to primary health centers. A total of 3,605 TB patients were enrolled in program in Morocco's five prefectures (Khemisset, Skhirat-Témara, Rabat, Salé, Kénitra) from January 2018 to December 2019. Smart Pillboxes were distributed only to high-risk TB patients along with the patient education conducted in various ways. Peer group learning was recommended for TB patients with high health illiteracy. One-on-one educations with psychosocial support were provided to patients with low socio-economic status, drug addiction, domestic violence, and family rejection.

Characteristics/outcomes	TB patients in rural area (n = 777, 21.6%)	TB patients in urban area (n = 2828, 78.4%)	TB patients in both area (n = 3605)
SEX n (%)			
Male	481 (61.9%)	1775 (62.8%)	2256 (62.6%)
Age (year) mean (SD)	36.94 (18.8)	37.58 (55.5)	37.44 (50)
TB outcomes n (%)			
* Reporting three outcomes as below	251 (32.3%)	1157 (40.9%)	1408 (39%)
Cured			
Treatment finish	476 (61.3%)	1478 (52.3%)	1954 (54.2%)
Lost to follow-up	36 (4.6%)	112 (4%)	148 (4.1%)
mHealth outcomes n (%)			
Patients with smart pillbox	62 (8%)	165 (6%)	227 (6%)

[Table.]

**Results/Impact:** The patients enrolled in our program were 62.6% male. The rate of successful treatment was 93.2%, which was higher than the 84% of Morocco's

existing treatment success rate. The lost to follow-up rate was 4.1%, significantly lower than the existing non-adherence rate of 7.9%. In a previous study, the lost to follow-up rate was significantly lower in the mHealth group than in the control group (OR:0.03,  $P<0.001$ ).

**Conclusions:** The integration of technology and the patient-centered approach to TB management were effective. This comprehensive approach provides an alternative method in countries with limited resources.

### EP22-314-23 The effect of digital dosing monitoring upon the adherence of patients treated for tuberculosis in Vietnam

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**Background:** Non-adherence is an important risk factor for relapse among patients with tuberculosis. In many healthcare systems, patients are required to self-administer therapy, potentially resulting in missed doses and poor treatment outcomes. This study evaluated the effect of digital adherence support, using a Medication Event Reminder Monitor (MERM), for outpatients treated for newly diagnosed smear positive pulmonary tuberculosis in Vietnam.

**Design/Methods:** A parallel-arm randomised controlled trial was conducted among 250 outpatients with newly diagnosed smear positive pulmonary tuberculosis treated in Thanh Hoa province, Vietnam. Patients in the intervention arm were provided a MERM box, equipped with a daily alert when a dose is due. Adherence data collected by the device was used to counsel patients about their adherence during the following month. Patients in the control arm received standard self-administered therapy, delivered in a MERM box without alarm.

Outcomes included the proportion of individuals with adequate adherence (defined as missing less than 20% of doses per month) and treatment outcomes.



[Figure 1. The proportion of patients with Tuberculosis with adequate adherence]

**Results:** We recruited 124 patients allocated to the intervention arm and 126 patients were allocated to the control arm. The adherence rate in the first month among patients in both arms was similar (87%), and started declining from the second month. From the third to fifth months, the intervention was associated with a 14%-19% increase in adherence compared to control arm. In the sixth month, the difference in adherence rate was 11.4% (68.9% patients in the intervention arm and 57.4% in the control arm). There was no difference in reported treatment completion between the two arms.

**Conclusions:** The use of digital daily reminders coupled with individual patient counselling improved adherence among patients with tuberculosis. Treatment adherence was poor in the final months of treatment. Low levels of adherence were not detected through routine treatment outcome reporting.

### EP22-315-23 Impact of health-related quality of life on treatment adherence during treatment for pulmonary tuberculosis

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**Background:** Poor health-related quality of life (HRQoL) in individuals with tuberculosis (TB) may adversely affect treatment outcomes by reducing medication adherence. We explore the impact of poor HRQoL at the start of treatment on adherence.

**Design/Methods:** Ongoing observational cohort study among adult patients receiving treatment for TB through national TB programs in The Gambia, Mozambique, South Africa, and Tanzania. We included patients with drug-susceptible pulmonary TB recruited between 07/2017-09/2019. HRQoL was measured



using the Medical Outcomes Short Form-36 (SF-36) questionnaire. Adherence was measured indirectly using patient self-report or directly observed treatment (DOT). We identified factors associated with suboptimal adherence (defined as missing a TB treatment dose at some point during TB treatment) using log-binomial regression.

Risk factors assessed included age, gender, HIV status and CD4 count, smear status and patient category (new or retreatment). Those with significant results are presented.

**Results:** 1085 patients were included in the analysis (median age 34years (IQR 28-43), 35.6% female, 40.8% HIV-positive, 88.9% smear-positive). At the start of treatment, the median (IQR) total SF-36 score was 38.4 (32.1-42.1), the physical component summary score (PCS) was 36.4 (30.2-44.3), and the mental component summary score (MCS) was 43.8 (27.6-57.2) – all lower than scores for the general population.

	All (n=1085)	Not included* (n=114)	Included (n=971)	n% (%) with outcome	Crude RR (95% CI)	Adjusted RR** (95% CI)
<b>Sex</b>						
Female	407 (31.8%)	31 (27.2%)	386 (39.6%)	11766 (8.0%)	0.9	1.0
Male	742 (62.1%)	48 (42.2%)	697 (64.2%)	9684 (12.2%)	1.4 (1.2-2.0)	1.7 (1.2-2.5)
Missing	37 (3.1%)	35 (30.7%)	2 (0.2%)	9 (0.0%)	-	-
<b>HIV status and CD4 count at initiation</b>						
HIV+ve CD4 >200	223 (18.8%)	27 (23.7%)	196 (18.2%)	13198 (7.9%)	0.8	1.0
HIV+ve CD4 100-200	180 (15.3%)	6 (5.3%)	174 (16.2%)	10076 (6.9%)	0.9 (0.8-1.0)	0.9 (0.8-1.0)
HIV+ve CD4 <100	41 (3.4%)	4 (3.5%)	37 (3.5%)	2039 (1.2%)	1.7 (0.7-4.4)	2.0 (0.8-5.1)
HIV negative	807 (67.7%)	28 (24.6%)	779 (74.7%)	30059 (13.8%)	2.1 (1.2-3.3)	2.0 (1.2-3.4)
<b>Smear status at initiation</b>						
Smear+ve (n=8)	393 (34.8%)	52 (45.6%)	341 (34.2%)	33252 (9.9%)	0.8	1.0
Smear-ve (n=8)	41 (4.1%)	52 (41.6%)	362 (38.2%)	26762 (11.8%)	1.4 (1.0-1.9)	1.4 (1.0-1.9)

Table 1. Demographics and clinical characteristics associated with suboptimal adherence]

Roughly 12% of patients (130/1085) reported suboptimal adherence. In adjusted analysis, males (aRR1.7, 95%CI:1.1-2.5) and those with poor PCS at treatment initiation (aRR1.4, 95%CI:1.0-1.9) were more likely to report suboptimal adherence. HIV negative patients also had an increased risk (aRR2.0, 95%CI:1.2-3.4) being that HIV infection is known to improve adherence to TB treatment.

**Background and challenges to implementation:** Poor health-related quality of life (HRQoL) in individuals with tuberculosis (TB) may adversely affect treatment outcomes by reducing medication adherence. We explore the impact of poor HRQoL at the start of treatment on adherence.

**Intervention or response:** Ongoing observational cohort study among adult patients receiving treatment for TB through national TB programs in The Gambia, Mozambique, South Africa, and Tanzania. We included patients with drug-susceptible pulmonary TB recruited between 07/2017-09/2019. HRQoL was measured using the Medical Outcomes Short Form-36 (SF-36) questionnaire. Adherence was measured indirectly using patient self-report or directly observed treatment (DOT).

We identified factors associated with suboptimal adherence (defined as missing a TB treatment dose at some point during TB treatment) using log-binomial regression. Risk factors assessed included age, gender, HIV

status and CD4 count, smear status and patient category (new or retreatment). Those with significant results are presented.

**Results/Impact:** 1085 patients were included in the analysis (median age 34years (IQR 28-43), 35.6% female, 40.8% HIV-positive, 88.9% smear-positive). At the start of treatment, the median (IQR) total SF-36 score was 38.4 (32.1-42.1), the physical component summary score (PCS) was 36.4 (30.2-44.3), and the mental component summary score (MCS) was 43.8 (27.6-57.2) – all lower than scores for the general population. Roughly 12% of patients (130/1085) reported suboptimal adherence. In adjusted analysis, males (aRR1.7, 95%CI:1.1-2.5) and those with poor PCS at treatment initiation (aRR1.4, 95%CI:1.0-1.9) were more likely to report suboptimal adherence. HIV negative patients also had an increased risk (aRR2.0, 95%CI:1.2-3.4) being that HIV infection is known to improve adherence to TB treatment.

**Conclusions:** Having a poorer quality of life, characterized by low physical function at the start of TB treatment, increased the risk of suboptimal adherence. Since HRQOL is one of the few determinants of adherence that can be addressed through interventions, improving HRQOL requires more attention.

### EP22-316-23 Evaluation of the integrated MDR/RR-TB patient management approach implemented in Wuhan Jinyintan Hospital, Hubei Province, China

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**Background:** Treatment adherence is critical to successful outcomes, but adherence to multidrug-resistant tuberculosis (MDR-TB) treatment is complicated by long regimens, disease severity, and both psychiatric and non-psychiatric side effects. In China, MDR-TB patients are usually hospitalized for the first 2 months of the initial 6 month intensive phase, and complete treatment as outpatients. They receive monthly treatment monitoring during the outpatient intensive phase and every other month thereafter. Jinyintan Hospital (JYTH) in Wuhan, China compared three care approaches to strengthen MDR-TB outpatient treatment adherence.

**Design/Methods:** JYTH used an electronic clinical management system to retrospectively analyze year one patient data from: 134 patients initiated on treatment in 2017 and provided with clinical care only; 179 patients in 2018 provided with clinical care and follow-up support (through hospital-CDC collaboration); and 199 patients in 2019 provided clinical care and follow-up support, and facility-based ancillary care. Chi square tests



were used to compare cohort performance across four interim outcomes: average monthly check-up rate (actual patient visits/scheduled visits), sputum culture rate (actual patient sputum testing/scheduled patient sputum testing), culture conversion rate, and patient retention rate (patients continuing treatment/patients initiated on treatment).

**Results:** The average monthly check-up rate was 43.33% in 2017, 65.33% in 2018, and 76.19% in 2019 ( $P < 0.001$ ,  $\chi^2 = 354.0608$ ) cohorts. The percentage of patients who completed scheduled sputum tests was 47.28% in 2017, 71.52% in 2018, and 97.63% in 2019 ( $P < 0.001$ ,  $\chi^2 = 690.2201$ ). Culture conversion rates at month 6 were 81.63% in 2017, 95.28% in 2018, and 94.52% in 2019 ( $P = 0.0062$ ,  $\chi^2 = 10.1631$ ). Patient retention rates were 56.72% for 2017, 79.05% in 2018, and 99.43% in 2019 ( $P < 0.001$ ,  $\chi^2 = 78.2609$ ).

**Conclusions:** This study documented that a comprehensive patient-centered model of care leads to improved adherence. As a result of this and other studies, the integrated patient-centered management approach is currently being scaled up across China to improve MDR-TB treatment adherence.

### EP22-317-23 Peer empowerment to strengthen treatment adherence among MDR-TB patients: field experience in Shaanxi Province, China

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**Background and challenges to implementation:** China has a high burden of MDR-TB. Qualitative studies showed insufficient social support was one of the key barriers to MDR-TB treatment adherence. In China, patients received limited psychosocial support from overburdened TB care providers. Lacking training and effective organization, spontaneous peer support among MDR-TB patients remained weak. Xi'an Chest Hospital (XCH) established a peer support group (PSG) for MDR-TB patients in Shaanxi Province, China.

**Intervention or response:** From July 2019 to February 2020, XCH recruited and trained 25 MDR-TB patients as peer educators. Training topics included achieving MDR-TB treatment success, managing daily medications and adverse drug reactions, the importance of treatment monitoring visits, nutritious diet, effective communication skills and expected roles and responsibilities. Trained peer educators conducted treatment education and psychosocial support through internet social media groups. They also helped provide facility-based care, including directly observed therapy for inpatients, peer counselling and small group thematic sessions.

**Results/Impact:** The peer educators conducted 670 individual counseling sessions and 82 group discussions reaching 640 MDR-TB patients. The intervention group

of 156 MDR-TB patients newly enrolled between August 2019 and January 2020 performed better than a historical baseline group of 134 MDR-TB patients between August 2018 and January 2019 on patient retention (95.5% vs. 79.1%,  $p < 0.001$ ) and loss to follow-up (3.2% vs. 18.7%,  $p < 0.001$ ). Qualitative results indicated positive changes after the intervention: MDR-TB patients exposed to peer support reported increased knowledge and self-efficacy for treatment adherence to reach cure; peer educators said they experienced greater fulfillment from helping others; and doctors reported it easier to communicate with patients and secure treatment compliance.

**Conclusions:** XCH successfully empowered PSG to support ancillary care for MDR-TB patients. Peer-led experiential learning and psychosocial support motivated active patient engagement in treatment preparedness and the making and adaptation of their individual treatment plans. PSG bridged communication and trust gaps between care providers and patients.

### EP22-318-23 Diverse patterns of tuberculosis medication adherence seen via directly observed therapy in an observational cohort

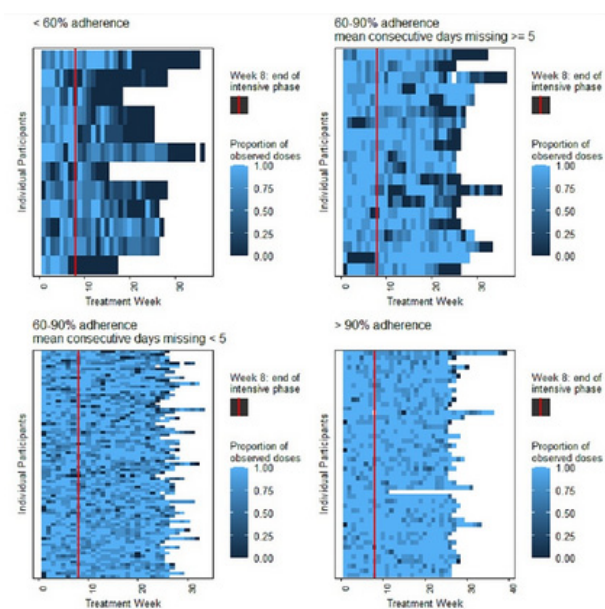
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**Background:** Tuberculosis (TB) therapy adherence patterns under directly observed therapy (DOT) are underreported. Understanding patterns and predictors of poor adherence, treatment interruptions, and loss to follow-up are critical in developing participant-specific adherence interventions and new regimens.

**Design/Methods:** We analyzed DOT data from participants enrolled in a prospective drug-susceptible TB cohort study from May 2017 - July 2019. We defined overall adherence to DOT as the number of observed doses over the course of treatment, excluding weekends

and holidays, and assuming observed doses during hospitalizations. We inspected weekly adherence patterns to DOT of four adherence groups: <60%, 60-90% with short interruptions (average consecutive missed DOT days <5), 60-90% with long interruptions (average consecutive missed DOT days  $\geq$  5), and >90%. We evaluated the difference in DOT adherence between intensive and continuation phases.

**Results:** For 160 participants, median overall adherence to DOT was 79.9%. Of the four DOT adherence groups, 12 (7.3%) participants had <60% adherence, 79 (47.9%) had 60-90% adherence with short interruptions, 20 (12.1%) had 60-90% adherence with long interruptions, and 49 (29.7%) had >90% adherence (Figure 1). Participants missed 54% more DOT days during the continuation phase of TB treatment than during the intensive phase. Participants with 60-90% overall adherence to DOT showed two distinct patterns: 79.8% (79/99) consistently missed DOT doses each week (short interruptions) and 20.2% (20/99) had sporadic longer interruptions of DOT (long interruptions).



Acronyms: TB- Tuberculosis, DOT- Directly observed therapy.  
Definitions: Mean consecutive days missing- when a participant misses a dose, on average, how many doses are consecutively missed afterward; Adherence- average overall adherence during treatment course; Proportion of observed doses- weekly number of observed doses by total number of weekdays (excluding holidays)  
Blank/white space indicates no DOT attempt made

[Figure 1. Distinct patterns of TB medication adherence under DOT (N=160)]

**Conclusions:** Using overall percentage of doses as the sole marker of adherence fails to capture the variation in patterns of adherence. We identified two distinct patterns of treatment interruption: shorter, more frequent interruptions and longer, infrequent interruptions. Different factors likely drive shorter versus longer interruptions, which are important to understand in developing new adherence interventions. These differing patterns may also differentially effect treatment outcomes even if overall adherence percentage is the same.

## EP23 TB in children and adolescents

### EP23-319-23 Chest-X-ray for tuberculosis diagnosis in children under 5 years living with a person with bacteriologically confirmed pulmonary tuberculosis in Africa: quality, inter-reader agreement and performances

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**Background:** To evaluate quality, inter-reader agreement and performances of chest X-ray (CXR) for tuberculosis (TB) diagnosis in children under 5 years living with a person with bacteriologically confirmed pulmonary tuberculosis as part of a contact investigation study using systematic CXR.

**Design/Methods:** The study was implemented in 3 countries. CXR were read locally by district hospital doctors in Benin and Burkina Faso, and by a pediatrician in CAR. A random sample of CXR was selected and reviewed by three independent reviewers. Quality of CXR was evaluated and interpretable CXR were identified. The inter-reader agreement with the local interpretation was assessed using the Kappa coefficient. Performances of local interpretation were evaluated using the TB diagnosis established by national study pediatricians as the reference. Analyses were performed with Stata software.

**Results:** Among the 499 CXR randomly selected, 445 (89.2%) were reviewed. Inadequate rotation, penetration and inspiration was found respectively for 18.5%, 25.5% and 23.2% of CXR and 393 (88.3%) were fully interpretable. The kappa for inter-reader agreement was 0.13 with large differences between countries (0.11 in Benin, 0.27 in Burkina Faso and -0.05 in CAR). The performances [95% CI] of the local CXR interpretation for TB diagnostic found sensitivity of 79.6% [65.7 – 89.8],

specificity of 85.1% [83.1–87.0], positive predictive value of 16.5% [12–21.9] and negative predictive value of 99.1% [98.4–99.6].

**Conclusions:** These results indicate low technical quality and poor-to-slight inter-reader agreement of CXR interpretation in young children in resource-limited settings in Africa. Performances of CXR for TB diagnosis appear very low in the context of contact investigation among generally healthy children. Screening young children for TB with CXR would need strong improvements including generalized implementation of clinical screening algorithms, access to digital X-Ray, reinforcement of the training of health care workers for CXR interpretation and the potential benefits of artificial intelligence for CXR interpretation.

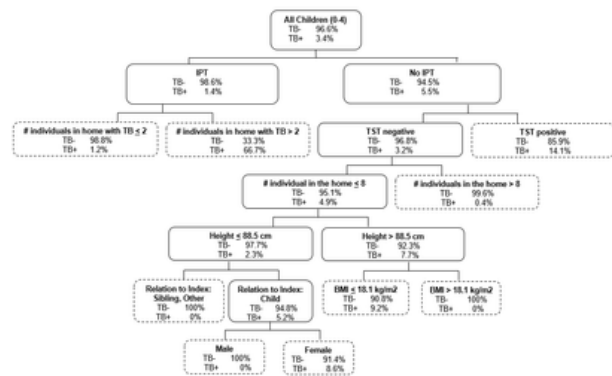
### EP23-320-23 Classification and regression trees to predict tuberculosis disease in children

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**Background:** The diagnosis of tuberculosis disease in children is complicated by nonspecific symptoms and low sensitivity of conventional diagnostic tests. Adult diagnostic algorithms applied in children result in underdiagnoses or missed cases. We sought to identify and rank in order of importance the predictors of tuberculosis disease in children who were exposed at home to tuberculosis.

**Design/Methods:** Between 2009 and 2012 in Lima, Peru, we conducted a prospective cohort study of children and adults who were living with adults diagnosed with pulmonary tuberculosis. Here we use classification and regression tree (CART) analysis to examine all potential predictors of incident tuberculosis disease in three age groups of children (0-4, 5-9, 10-14 years old). CART uses recursive partitioning and variable importance measures to select predictors that give the best discrimination between the two outcome classes. We calculate the risk ratio for each of the top predictors.

**Results:** Among 4,545 children 0-14 years of age, 156 (3.4%) were diagnosed with tuberculosis disease within a year of being exposed at home (3.4%, 2.3%, and 4.7% in children 0-4, 5-9, and 10-14 years old, respectively). The primary node (or most important predictor) in the 0-4 years model was use of isoniazid preventive therapy (RR 0.26; 95% CI: 0.14-0.48) [Figure 1]. Having <5 individuals living in the home who are TST+ (RR: 0.28, 95% CI: 0.14-0.56) and the child being TST+ (RR: 2.64, 95% CI: 1.60-4.34) were the primary predictors for the 5-9 and 10-14 year models, respectively.



[Figure 1.]

**Conclusions:** Predictors of tuberculosis disease among children exposed at home to tuberculosis vary by age stratum. CART searches through all potential predictors and cutoff values to identify the best predictor for accurately classifying children with TB disease. Simple trees can be further developed for validation at health facilities to generate useful clinical tools to classify TB in children exposed at home.

### EP23-321-23 Epidemiology and clinical manifestations of adolescent tuberculosis in Ukraine

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**Background:** During adolescence, childhood and adult forms of tuberculosis (TB) overlap, resulting in a diversity of presentations. Knowing which patient characteristics are associated with distinct disease manifestations may facilitate diagnosis and enhance understanding of the pathophysiology of adolescent TB.

**Design/Methods:** Using data from Ukraine's national TB registry, we conducted a cross-sectional study of 10-19-year-olds who started TB treatment between January 2015-November 2018. Using logistic regression, we estimated associations between patient characteristics at diagnosis and four presentations of TB: pleural, extra-thoracic, cavitary, and rifampicin-resistant (RR).

**Results:** During the study period, 2491 adolescent TB cases were notified in Ukraine. Pleural disease was more common among males than females, but only in the 10-14 year age group (adjusted odds ratio [aOR] 2.12, 95% confidence interval [CI]: 1.08-4.37). Extrathoracic TB was less common among 15-19-year-olds (aOR 0.26, 95% CI: 0.18-0.37) and more common among HIV-infected participants (aOR 3.25, 95% CI: 1.55-6.61 in 10-14-year-olds; aOR 8.18, 95% CI: 3.58-17.31 in 15-19-year-olds).

Cavitary TB was associated with age 15-19 years (aOR 4.10, 95% CI: 3.00-5.73) and, in 15-19 year-olds only, inversely associated with human immunodeficiency virus infection (aOR 0.32, 95% CI 0.13-0.70). RR-TB was associated with recurrent TB (aOR 1.87, 95% CI: 1.08-3.13) and cavitary TB (aOR 2.98, 95% CI: 2.35-3.78). RR-TB was inversely associated with pleural TB (aOR 0.44, 95% CI 0.25-0.74).

**Conclusions:** Age, sex, HIV status, and prior TB treatment impact the presentation of adolescent TB in Ukraine. Preventive, diagnostic, and treatment activities targeting this age group should take these factors into consideration.

### EP23-322-23 Prevalence and predictive factors of active tuberculosis in children under 5 years living with a person with bacteriologically confirmed pulmonary tuberculosis in Africa

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**Background:** To determine the prevalence and predictive factors of active tuberculosis in children under 5 years living with a person with bacteriologically confirmed pulmonary tuberculosis (BCPT) during the home visit as part of a contact investigation study.

**Design/Methods:** The study was implemented in 4 countries: Benin, Burkina Faso, Cameroon, Central African Republic. Children were evaluated during home and clinic visits using standardized questionnaire, clinical examination, tuberculin skin test and chest X-ray. The outcome was the diagnostic of TB established by

national study pediatricians. Independent variables included the characteristics of index cases (age, gender, HIV status, occupation, education, household characteristic, economic level, cough duration) and the contacts (age, gender, BCG vaccination, exposition factors to index cases, link with index cases, clinical signs). After univariate analyses, a multivariate logistic regression was performed and all variables significant at 25% were included.

**Results:** One thousand and seventy-six (1076) index cases were included for a total of 1965 children. The mean age of children was 30.43 ± 17.57 months and 978 (49.8%) were female. Prevalence of TB was 2.8% in children. Multivariate analysis found that female children, children with lymphadenopathy and children with poor health condition had a significantly higher risk to have TB (OR = 1.86 [1.04-3.33], OR=3.73 [1.92-7.26] and OR=3.34 [1.51-7.42], respectively). We also found that children in contact with female index cases, children whose have a direct link (son or daughter) with index cases and children in contact with index cases who cough more than one month had a significantly higher risk to develop TB (OR = 1.76 [1.00-3.10], OR=1.98 [1.11-3.53], OR = 1.60[1.05-2.44], respectively).

**Conclusions:** The predictive factors of active TB in children living with BCPT identified in this study could be used to propose a score for TB screening during the home visit in African countries.

### EP23-323-23 Childhood tuberculosis trends in Zambia over five years (2014-2019)

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**Background and challenges to implementation:** Globally, Childhood Tuberculosis (TB) for a long time had been neglected. In the recent years, there has been renewed commitment to the childhood TB agenda based on the resounding clarion call from the World Health Organization, WHO through National Tuberculosis Programmes, NTP's and relevant actors to step up the Child TB response. Zambia, through its Ministry of Health, MoH and its partners is responding.

**Intervention or response:** We conducted national and sub-national retrospective program data desk reviews for NTP notifications filtering childhood TB reported

data by WHO proposed age disaggregation for the period 2015 to 2019. The abstracted data was then cross referenced with total notifications to ascertain congruity with expected childhood notification proportions (10-15%) in line with WHO childhood TB epi-estimates.

**Results/Impact:** There was a decline of 0.4% in all forms childhood TB case notifications as a proportion of overall TB notifications from 2015, (6.1% {2,518/41,279}) to 2016 (5.7% {2,293/40,228}). There was a steady rise in childhood TB cases from 2016 to 2019 (7% {2,498/36,844}) with a net increase of 1.3%. There was huge variation in childhood TB notifications as a proportion of overall notifications in 2019 (4 to 11%) and one of the postulations is under reporting as evidenced by a nationwide data quality audit that undertaken by the NTP in that year.

Despite aggregated Zambia childhood TB notifications showing a rising trend, of concern, are low observed Childhood TB notifications in the two overall highest notifying provinces: Copperbelt (4% {347/8,384}) and Lusaka (6% {753/13,509}).

**Conclusions:** Increasing childhood TB notifications in 2016 to 2019 can in part be attributed to country wide training (childhood TB formulations and diagnosis in children) coordinated by the NTP and partners coupled with follow on mentorship.

Robust contact tracing, novel diagnostics: gene Xpert ultra, interferon gold, computer aided diagnosis and increased overall case detection is paramount.

### EP23-324-23 Routine South African tuberculosis data: are we doing enough for children and adolescents?

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**Background:** Although children and adolescents with tuberculosis (TB) are globally recognised as important key populations, there are currently limited approaches to evaluate how well TB programmes address TB control in these groups.

We used routine data to analyse TB case notification indicators disaggregated by age, and discuss South Africa's progress over a 13-year period for TB in children and adolescents.

**Design/Methods:** All newly registered children and adolescents treated for drug-susceptible TB in a cleaned, de-duplicated national electronic TB treatment register (ETR.Net) dataset (2004-2016) were included. TB case notification rates (CNRs) and TB-HIV co-infection prevalence were calculated in four age bands: 0-4, 5-9, 10-14 and 15-19 years.

**Results:** Overall, 720,251 children and adolescents (0-4: 339,534 [47%]; 5-9: 131,551 [18%]; 10-14: 72,864 [10%]; 15-19: 176,302 [25%]) were treated for TB in South Africa 2004-2016. TB CNRs in all age bands peaked during 2008/2009, ranging from 152/100,000 in 10-14 year olds in 2009, to 635/100,000 in 0-4 year olds in 2008. The percentage point reduction in CNRs between 2009 and 2016 varied by age: 0-4: -59%, 5-9: -72%; 10-14: -46%; 15-19: -28%. In all age groups, HIV status was known for >80% of cases since 2013. In 2016, HIV co-infection ranged from 15% in 0-4 year olds, to 43% in 10-15 year olds.

**Conclusions:** The TB burden and prevalence of HIV co-infection amongst children and adolescents in South Africa remain high. Reduction in TB CNRs has been the lowest in adolescents, especially in 15-19 year olds. There was substantial variation in routine indicators when data were dis-aggregated into smaller age bands. These differences are obscured in the currently reported age categories. Analysis and reporting by smaller age bands could provide actionable data to TB programmes to better understand and respond appropriately to children of all ages affected by TB and by HIV.

### EP24 TB innovative strategies to find the missing cases

#### EP24-325-23 Engaging Patient Medical Vendors (PMVs) in TB case finding: the Pros and Cons

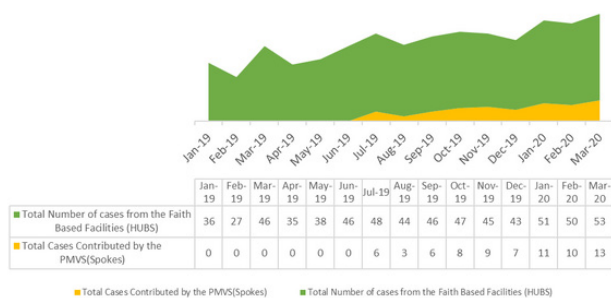
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**Background and challenges to implementation:** Available local data suggests that about 60% of persons with cough and other ailments seek care from the patient medical vendors (PMVs), Caritas Nigeria Funded by the Global Fund public private Mix Grant sought to intensify case finding through engagement of PMVs for active case finding in the community.

This work reviews the PMVs Engagement processes, their contribution to case finding and challenges encountered.

**Intervention or response:** Pre-implementation activities commenced in March 2019. when a baseline assessment of all faith-based health facilities was carried out using national health facility assessment tools. Thereafter, contiguous PMVs outlets (10 – 15) were linked to the hospitals in a ‘Hub-And-Spokes’ approach. Implementation proper started in July 2019 after training of the PMVS and Faith based facilities. Presumptive TB cases identified by the PMVs were referred to the hub facilities for diagnosis and treatment. Linkage coordinators were trained and engaged to move samples from the PMVs to the identified Xpert MTB/RIF testing labs and also give feedback to the PMVs. Monetary Incentives were provided to PMVs, about \$0.3 for a presumptive case and \$3.0 for a confirmed TB case.

**Results/Impact:** The number of TB cases reported by the Hub facilities per month increased by 29.7% from a pre-implementation average of 37 cases/month to 48 TB cases/month within the implementation period. Additionally the PMVs (spokes) contributed a total of 73 TB cases representing 17% of all cases reported by the hubs. TB Cases found by PMVs (spokes) and Faith-based hospitals (HUBS) January 2019 - March 2020 in Anambra state, Nigeria.



[Figure.]

**Conclusions:** Engagement of the PMVs through their Organization helped to break the barrier of suspicion and increased their participation in Active TB case search, weekly reminders through phone calls and text messages contributed to the success of the intervention. Informal providers remain important stakeholders towards finding the missing TB cases in Nigeria.

**EP24-326-23 Enhancing TB diagnosis among unengaged, standalone, formal and informal private health facilities in finding missing people with tuberculosis in Kenya**

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**Background and challenges to implementation:** Tuberculosis (TB) is the fourth leading cause of death in Kenya. In 2016, the health system missed almost 50% of people with TB. About 48% of health facilities in Kenya are private and serve 42% of people who seeking health services as the initial point of care. However, private sector contribution to TB case finding was only 15% in 2019 against a target of 25%. The sector is faced by a myriad of Challenges include; knowledge gaps among the providers, poor linkage systems, poor recording and reporting among others.

**Intervention or response:** Mapping and prioritization of private providers was carried out. Providers were trained using national TB curriculum. Recording and reporting tools were customised, printed and distributed, sample transport mechanism was put in place. ‘Hub and Spoke’ model was used to link the providers (Spokes) to the diagnostic sites (hubs). Community Health Volunteers were engaged to strengthen feedback of results from the hub and linkages of patients to treatment sites. Providers carried out TB screening, diagnosis and referral. Incentivization done based on new TB cases.

**Results/Impact:** Since August 2019, a total of 1,168 private providers were mapped including clinics, pharmacies and laboratories. 538 were selected for engagement based on set criteria and 318 providers trained on TB. A total of 411 facilities have consistently reported for the past 6 month. 40,362 people have been screened for TB, 3, 277 were presumed to have TB, 1, 811 among them tested, 133 diagnosed with TB and started on treatment. **Conclusions:** Meaningful engagement and support of private providers is key to finding the missing people with TB. There is need to continuously build the capacity of the private providers, strengthen access to diagnostic services and address recording and reporting gaps.



### EP24-327-23 The role of community-based interventions to reach out to underserved populations and increase the success rate of TB treatment in Gaza Province, Mozambique, 2019

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**Background:** The low case detection and the barriers to access diagnosis and treatment of TB underpin the transmission within communities, particularly among underserved and high-risk groups (World Health Organization, 2017). This study evaluated a community-based active case finding strategy, among the general population and high-risk groups in Gaza, South of Mozambique in 2019.

**Design/Methods:** This is a retrospective cohort study carried out in Gaza Province, in Mozambique, aiming to compare the yields of passive (PCF) versus active (ACF) case finding in 2019. The ACF approach was:

1. Screen for TB symptoms among household's contacts and the general population by home visits and high-risk people such as co-infected TB/HIV, households contacts, children and miners or ex-miners. The screening is conducted by trained community health workers.
2. The presumptive cases underwent sputum microscopy/molecular confirmation.

TB case notification rates were computed to evaluate the ACF strategy compared to PCF and the programmatic performance before the ACF. Chi-square test was applied to assess statistical significance and incidence proportions to access the effect of ACF on high-risk groups.

**Results:** Of the 22114 that were screened for TB symptoms, 11.4 % were presumptive cases and 639 (out of 1901) TB cases were detected. There is a significant difference between case notifications between ACF (679 per 100,000) and PCF (382 per 100,000) (RR=1.7;95% CI: 1.7-1.9) during the period of analysis.

On the treatment outcomes, the ACF has contributed to the reduction, in 2019, of TB related death risk from RR of 0.6 to 0.4 (95% CI: 0.2-0.9) either in general or among HIV/TB patients.

**Background and challenges to implementation:** The low case detection and the barriers to access diagnosis and treatment of TB underpin the transmission within communities, particularly among underserved and high-risk groups (World Health Organization, 2017). This study evaluated a community-based active case finding strategy, among the general population and high-risk groups in Gaza, South of Mozambique in 2019.

**Intervention or response:** This is a retrospective cohort study carried out in Gaza Province, in Mozambique, aiming to compare the yields of passive (PCF) versus active (ACF) case finding in 2019. The ACF approach was:

1. Screen for TB symptoms among household's contacts and the general population by home visits and high-risk people such as co-infected TB/HIV, households contacts, children and miners or ex-miners. The screening is conducted by trained community health workers.

2. The presumptive cases underwent sputum microscopy/molecular confirmation.

TB case notification rates were computed to evaluate the ACF strategy compared to PCF and the programmatic performance before the ACF. Chi-square test was applied to assess statistical significance and incidence proportions to access the effect of ACF on high-risk groups.

**Conclusions:** The community engagement through ACF is a key strategy to address issues of access and to reach underserved and hard-to-reach communities and increase the treatment outcomes.

### EP24-328-23 TB active case finding in fragile post conflict areas in Darfur, Sudan

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**Background and challenges to implementation:** North Darfur state AL Malha locality was one of the most affected localities with Darfur conflict, it distances about 250 Km from the state capital, this conflict resulted in weak fragile health system in the whole states. Additionally, the locality population is 165548 and all lives in rural areas. Poverty and high illiteracy level are the character of the pastoral community. There is a one TB management unit (TBMU) covering the locality with zero report or less than 10 cases per year in the last decade.

**Intervention or response:** In 2017, for about 10 days, and on the behalf of the TB program the Epi-Lab conducted TB active case finding (TB-ACF) in Al Maliha locality, to reestablish the TB service and to increase the case finding. We started by training community volunteers to do door to door triage, and then the assessment of the presumptive from the community is done by doctor. LED microscopy was used for the screening. Finally, treatment was initiated for those whom tested positive after HIV testing.

**Results/Impact:** The total number of tested people was 272 having cough for more than 2 weeks, 30 of them was bacteriologically confirmed, all of them tested HIV negative and enrolled in treatment. All new patients were linked with the locality TBMU. Unfortunately, by the end of the year the state TB program and the national TB referral lab closed the TBMU and those patients remained with no treatment outcomes.



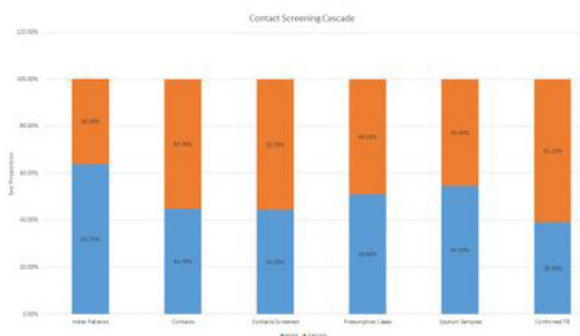
**Conclusions:** TB Active case finding is one of the strategies that is recommended to tackle the TB low notification or zero, but case holding throughout the treatment duration is essential part to stop the spread of the disease. Accordingly, we need to strengthen the TB service at the grass root level before adopting interventions such as TB-ACF because it resulted in un evaluated treatment outcome.

### EP24-329-23 Low male yield from community based TB contact tracing - experiences from community contact tracing in Lesotho

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**Background and challenges to implementation:** Lesotho has a high TB burden with an estimated prevalence of 695 cases per 100,000 population. Ongoing transmission is fueled by low treatment coverage (55%). With a male to female prevalence ratio of 1.8, males are disproportionately infected and sex disparities increase with age. Basotho men generally have a low affinity for health facilities and typically present late for treatment. Community TB contact tracing was adopted to promote early case detection and linkage to appropriate curative and prevention services.

**Intervention or response:** TB contact tracing in Lesotho's five highland districts is done by a team of 34 contact tracers (22 females and 12 males) using standardized national tools. Sputum samples are collected from presumptive cases at community level before temporarily storage at a health facility and transport to the nearest laboratory. Data on number of index clients, contacts listed, contacts screened, presumptive cases and new TB diagnoses was analyzed by age and sex. We defined an adult as older than 15 years. Information was collected from facility registers and reports for the period August 2019 to April 2020.



[Figure.]

**Results/Impact:** A total of 884 index clients were identified during the period under review from whom 4435 contacts were elicited and 4258 were found and screened for TB symptoms. One hundred and sixty three (163) contacts had TB presumptive signs and 18 were con-

firmed new TB cases. The large majority of adult index clients in this analysis were men (63.3%) but men contributed only 35.3% of adult cases identified through community contact tracing.

**Conclusions:** While the high proportion of men starting TB treatment in Lesotho's health facilities is in line with the estimated national TB prevalence sex ratio, adult males are clearly underrepresented among cases found through community TB contact tracing. Current community tracing and screening approaches must be refined to find missing men.

### EP24-330-23 Tuberculosis screening at Bungoma Bus Park, Bungoma County, Kenya

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**Background:** World Health Organization launched the End TB Strategy in 2015 with a goal of ending the global tuberculosis (TB) epidemic by 2035; this requires a dramatic improvement in current case-detection strategies. Prevalence survey done in Kenya showed that approximately 40% of TB cases are missed. Identification of high risk congregate communities or occupational risk environments that result in increased contact rates, exposure to highly infectious TB, or increased susceptibility to TB disease may lead to improved TB control. Bus crews especially the touts are hard to reach and at risk population because they are always on the move and work in crowded vehicle, they are also likely to interrupt treatment because of their highly mobile lifestyle. Public transport may serve as a catalyst for TB transmission. We aim to screen all people in Bungoma Bus Park.

**Design/Methods:** A mass screening exercise was organized targeting the drivers, touts, hawkers, mechanics and small scale business people within Bungoma Bus Park. Community mobilization was done. Screening was conducted by health care workers (HCW) using a structured questionnaire. All the presumptive cases produced sputum for GeneXpert.

**Results:** Total of 324 people were screened, 95/324 (29.3%) were presumptive TB cases, 86/95 (90.5%) produced sputum for GeneXpert, 8/86 (9.3%) were confirmed to have TB. Four of the 8 who had TB had started TB treatment previously but had interrupted treatment.

**Conclusions:** Targeted outreach in hard to reach and risk population is important. This can be used as a strategy for finding the missing TB cases, eventually reducing transmission of TB. Adherence counseling should be reinforced to reduce TB treatment interruption in this group.

## EP24-331-23 Yield and coverage of active case finding interventions for tuberculosis control in high-burden countries: a systematic review and meta-analysis

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**Background:** Active case finding (ACF) has had low priority in countries with a high burden of tuberculosis (TB), but is a key strategy to reduce diagnostic delays, expedite treatment, and prevent TB transmission. WHO estimated a global incidence of 10.0 million TB cases in 2018, of which only ≈70% were reported.

**Design/Methods:** We conducted a systematic review evaluating yield (i.e., proportion of those screened who had active TB) and coverage (i.e., proportion of those targeted who were screened) of different ACF approaches among individuals and communities in high-burden countries, identifying peer-reviewed studies published from 1980-2016 that reported ACF outcomes. We conducted meta-analyses and meta-regression with random effects models to identify populations, settings, WHO regions, and screening/diagnostic approaches for which yield and coverage were higher.

3.4%) and pooled coverage was 93.3% (95% CI 91.9%–94.5%). In meta-regression, the use of laboratory tests (microscopy, culture, or GeneXpert) for initial screening had significantly higher yield compared to studies using symptom screening (beta 3.5%, 95% CI 0.6%–6.4%). In addition, studies that used laboratory screening (usually microscopy) followed by diagnosis using culture or GeneXpert had higher yield than those using symptom screening followed by microscopy for diagnosis (beta 4.4%, 95% CI 0.9%–7.9%). In a model comparing approaches with and without GeneXpert, PLWH had higher yield versus general population (beta 5.1 95% CI 1.1%–9.2%). In all models, studies targeting children only had higher yield ( $p < 0.01$ ).

**Conclusions:** ACF yield was higher when implemented in health care settings and among high-risk populations such as PLWH and children. Scaling up screening algorithms that use laboratory tests for both screening and diagnosis increases yield compared to approaches using symptom screening and other methods.

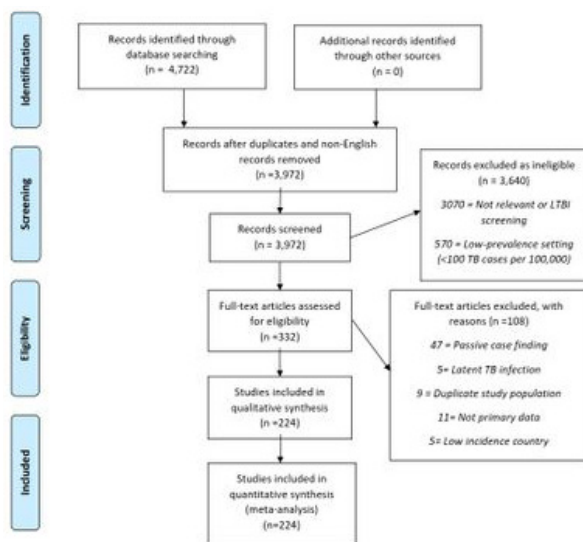
## EP24-332-23 An adaptive decision-making approach to efficiently deploy tuberculosis case finding in high-burden communities

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**Background:** Community-based active case finding (ACF) can help reduce diagnostic delay in tuberculosis (TB)-affected populations. Strategies are needed to target ACF towards communities with the highest burden of undetected TB to make best use of limited resources. We introduce an adaptive decision-making approach (ADMA) to allocate ACF resources to communities in the absence of data about the prevalence of undetected TB. We aimed to estimate the extent to which the ADMA could increase case-finding yield relative to a random ACF approach.

**Design/Methods:** The proposed ADMA uses a Bayesian sampling algorithm that updates prior beliefs about case-finding yield in different communities with data obtained during weekly ACF rounds. We developed a Monte-Carlo simulation of ACF using TB prevalence estimates for 24 South African and Zambian communities derived from a large community-randomized trial (Figure 1a). We considered a limited-resource scenario

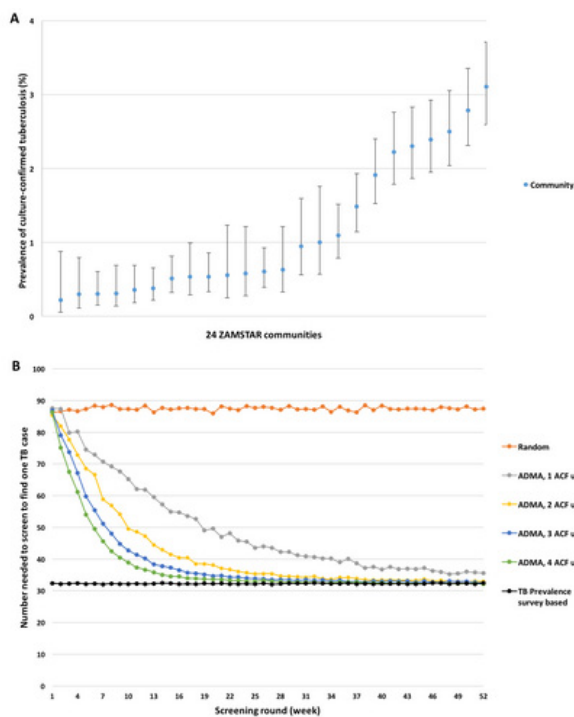


[Figure 1. Prisma diagram]

**Results:** Of 3,972 abstracts screened, 224 papers met criteria after full text review. The pooled yield of active TB was 3.2% (95% confidence interval [CI] 2.9%–

under which a pre-specified number of mobile ACF units would be allocated among the communities during a 52-week period. We used the simulation to investigate the expected case-finding yield under the ADMA compared to random allocation of ACF.

**Results:** We estimate that random allocation of four ACF units among the 24 communities would result in an expected annual yield of 11.4 (95% uncertainty interval 4.0-21.5) TB cases per 1,000 people screened. Dynamic allocation under the ADMA would increase this yield to 28.1 (23.7-34.2) TB cases per 1,000 people. Numbers needed to screen to find one TB case decreased more rapidly over time with increasing numbers of ACF units contributing to the Bayesian algorithm (Figure 1b).



[Figure 1a,b. Simulation of community-based active case finding (ACF) for tuberculosis (TB) in 24 African communities; (a) Estimates of community-level TB prevalence (adults, culture-confirmed TB) used for the simulation; the data were obtained from TB prevalence surveys that had been conducted as part of the Zambia South Africa TB and HIV Reduction (ZAMSTAR) study (see: Ayles et al., *The Lancet*, 2013), (b) Numbers needed to screen to find 1 TB case over time (weeks) obtained through simulation of different ACF strategies - random allocation of 4 ACF units among the communities, adaptive decision-making approach (ADMA)-based allocation with one to four ACF units available, and allocation of 4 ACF units to the community with the highest TB prevalence estimate, assuming that prevalence survey results would be available.]

**Conclusions:** We show that an adaptive approach to deploy ACF can significantly increase TB case-finding yield by dynamically targeting resources towards communities with the highest prevalence of undiagnosed TB. Further research is needed to understand how adaptive case-finding approaches could help reduce TB in high-burden settings.

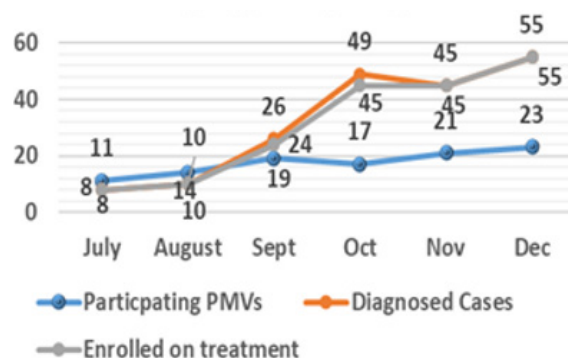
## EP24-333-23 Patent and propriety medicine vendor's led community engagement: an innovative approach to finding missing TB cases in rural communities in Boki Local government, Nigeria

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**Background and challenges to implementation:** Patent and Proprietary Medicine Vendors (PMVs) play a critical role in bridging the gaps in healthcare delivery especially among rural communities. Five “hub” and “spokes” clusters comprising fifty PMVs and five private health facilities were engaged to provide TB services supported by linkage coordinator (LC) assigned to five clusters. The study assesses the effectiveness of the PMVs led community mobilization using town announcers in finding missing TB cases.

**Intervention or response:** The PMVs and LC conducted advocacy to community leaders and used community town announcers at no additional cost to mobilize persons with a cough to the PMV's shops for free symptomatic TB screening. The presumptive TB identified were linked to TB diagnostic labs for sputum testing. The detailed information of the presumptive TB patients and their lab results were documented in the National TB recording and reporting tools. Lab results feedback was provided to the PMVs. Persons who had TB were contacted and linked to TB treatment at the hub facility. We documented the presumptive TB identified, TB cases diagnosed and participating PMVs/communities monthly from the commencement of intervention in September to Dec. 2019 and compared with previous months.

**Results/Impact:** In July and August 2019 the TB cases notified in the five clusters were 8 and 10 respectively. However, following the introduction of the intervention in September, TB case finding increased to 26 and further increased to 49, 45 and 55 cases in Oct, Nov. and December respectively. The overall linkage to TB treatment was above 95%.



[Figure. A six months trend analysis of case finding by participating PMVs]

**Conclusions:** PMVs knowledge of the community is a potential resource that can be harnessed to promote increased TB screening within the community. Using PMVs within the community in engaging the key community leaders and mobilizing the people through the traditional town announcers/criers is both cost-effective and innovative for finding missing TB cases.

## EP25 Lung health across the lifespan

### EP25-334-23 Effectiveness of the 10-valent pneumococcal conjugate vaccine (PCV) against radiographic pneumonia among children in rural Bangladesh: a case-control study

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**Background:** PCV effectiveness against radiographic pneumonia in South Asia is unknown. Bangladesh introduced PCV10 in 2015. We measured PCV10 effectiveness against radiographic pneumonia.

**Design/Methods:** We conducted a matched case-control study between 2015-2017 using clinic and community controls in Sylhet, Bangladesh. Cases were 3-35 month olds at Upazila Health Complex outpatient clinics with WHO-defined radiographic pneumonia. Clinic controls were matched to cases within one week by age, sex, and clinic and had a likely non-pneumococcal illness; healthy community controls were additionally matched by distance from the clinic. We estimated adjusted vaccine effectiveness (aVE) using conditional logistic regression.

**Results:** We matched 1,262 cases with 2,707 clinic and 2,461 community controls. Overall, aVE using clinic controls was 21.4% (95%CI, -0.2%, 38.4%) for >2 PCV10 doses and among 3-11 month olds was 47.3% (10.5%, 69.0%) for three doses. aVE using community controls was 7.6% (-22.2%, 30.0%) for >2 doses. Vaccine introduction was faster and less variable than expected, which reduced power. Information bias may have affected community controls.

**Conclusions:** Clinic control analyses show PCV10 prevented radiographic pneumonia, especially among younger children. Community control analyses were underpowered and control enrollment was challenging in a complex healthcare system. Similar future studies may consider clinic controls only.

### EP25-335-23 It's not TB but what could it be? Abnormalities on chest X-rays from the 2016 Kenya National Tuberculosis Prevalence Survey

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**Background:** The prevalence of diseases other than tuberculosis (TB) detected on chest-Xray (CXR) during TB screening in Kenya is unknown. Our study aimed to characterise and quantify non-TB abnormalities on CXR and to compare radiologist interpretation with Computer-Aided Detection for Tuberculosis (CAD4TB). We hypothesized that non-TB abnormalities requiring further clinical input are prevalent and may be missed using CAD4TB.

**Design/Methods:** We undertook a cross-sectional study from May 2019-February 2020, analyzing CXRs from the 2016 Kenya National TB Prevalence Survey, sampling films classified either as "abnormal, suggestive of TB" or "abnormal other". We developed a reporting tool which comprised four anatomical categories and a list of common diagnoses. Readers were blinded, films double reported and discordant results resolved by a third reader. We used CAD4TB 6.0. and R v3.6.2. for analysis.

**Results:** Of 1123 films sampled, 600 (53.4%) were abnormal (Figure-1). Prevalence of abnormalities in major categories: 26.3% (95% CI 23.7%-28.9%) heart and/or great vessels, 26.1% (95% CI 23.5%-28.8%) lung parenchyma, 7.6% (95% CI 6.1%-9.3%) pleura and 3% (95% CI 2.1%-4.2%) mediastinum. Prevalence of active-TB 4% (95% CI 2%-4%), severe post TB lung changes (bronchiectasis/destroyed lung) 2% (95% CI 0-2%). Non-TB related diagnoses: cardiomegaly 23.1% (95% CI 20.6%-25.6%), suspected cardiac failure 1.9% (95% CI 1.2-2.8%), non-specific airspace opacification/interstitial disease 6% (95% CI 4%-8%), suspected em-

physema 2% (95% CI 2%-4%) and mediastinal masses 0.8% (95% CI 0.4%-1.5%). Median CAD4TB scores: Severe post TB lung changes 76 (IQR 71-81), active-TB 66 (IQR 55-72), suspected emphysema 57 (IQR 54-59), non-specific airspace opacification/interstitial disease 56 (IQR 50-61), mediastinal mass 52 (IQR 47-59) and cardiomegaly 50 (IQR 46-56).

**Conclusions:** Abnormalities unrelated to TB were prevalent, most notably cardiomegaly. These non-TB abnormalities will go undetected using CAD stratification based on threshold scores alone. Further refinement of CAD algorithms to include non-TB diagnoses could attenuate this risk. Incorporation of blood pressure monitoring and spirometry should be considered in TB screening activities.

### EP25-336-23 Supplemental oxygen in Queen Elizabeth Central Hospital Malawi: a prospective cohort study of patients admitted to medical wards

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**Background:** Oxygen is listed as an essential drug by the World Health Organisation and has been shown to reduce mortality in the context of hypoxia. In low-resource settings the provision of oxygen seldom meets the demand. This study aims to explore the predictors and the observed time-course of hypoxaemia, and thus better rationalize distribution of oxygen therapy in lower-middle income countries.

**Design/Methods:** We conducted a prospective cohort study of adults with hypoxaemia that received oxygen therapy and were admitted to medical wards at a teaching hospital in Malawi between January and March 2020. Vital signs and oxygen therapy were recorded daily. Study end-points were death, discharge from hospital or continued inpatient at day 14. Kaplan-Meier and Cox regression analysis was used for time-to-event analysis.

**Results:** 33 patients were included in the study (median age 45 years [interquartile range (IQR) 33-61 years]). The median oxygen saturations at initiation of oxygen therapy was 84% (IQR 76-87%). Oxygen delivery devices were often shared with other patients (10 [33.3%]) and the flow rate was often unknown (14 [46.7%]), mostly because of broken equipment (8 [57%]).

The median length of time receiving oxygen therapy was 3 days (IQR 1-7 days). Death was the most common

end point (16 [48.5%]) and pneumonia the predominant final diagnosis (14 [42.4%]). The presence of a chest radiograph and being an ex- or never smoker had a reduced hazard of short oxygen therapy (HR 0.08, 95% CI 0.02 – 0.30; HR 0.01, 95% CI 0.00 – 0.22; HR 0.03, 95% CI 0.00 – 0.78 respectively).

**Conclusions:** The delivery of oxygen therapy in lower-middle income countries is challenging; there is a lack of functioning equipment to allow delivery of titrated oxygen therapy and limited resources result in devices being shared. Patients receiving oxygen in this setting were relatively young and at a high risk of death.

### EP25-337-23 Searching for microbiome predictors of poor outcomes among infants with respiratory syncytial virus-associated pneumonia in Botswana

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**Background:** Respiratory syncytial virus (RSV), the most common cause of childhood pneumonia, is the leading infectious cause of death among children worldwide. Most deaths occur in low- and middle-income countries, but predictors of poor outcomes in these settings are incompletely understood. Alterations in the upper respiratory microbiome are associated with susceptibility to lower respiratory viral infections, but the effect of these alterations on clinical outcomes in RSV-associated pneumonia is unknown. We endeavored to identify respiratory microbiome-related factors associated with clinical non-response among children hospitalized with RSV-associated pneumonia in Botswana.

**Design/Methods:** We enrolled children 1-23 months of age who met the World Health Organization (WHO) definition of clinical pneumonia and followed them until hospital discharge or death. Nasopharyngeal swabs were collected at enrollment for respiratory viral testing and sequencing of the V3 region of the bacterial 16S ribosomal RNA gene. Clinical non-response was defined as persistent chest wall indrawing, new WHO danger signs, hypoxemia, an ongoing requirement for positive pressure ventilation, or death.



**Results:** One hundred fifteen children were included in this analysis, 49 (42%) of whom met criteria for clinical non-response. Shannon diversity of the nasopharyngeal microbiota did not differ by treatment response status (multivariable linear regression;  $P=0.24$ ). Similarly, overall nasopharyngeal microbiome composition did not differ between children with clinical response and those with clinical non-response (PERMANOVA;  $P=0.17$ ). Lastly, using negative binomial regression, no differences were observed between patients with clinical response and those with clinical non-response. All analyses were adjusted for age, sex, and known risk factors for poor outcomes among children with pneumonia.

**Conclusions:** The composition of the upper respiratory microbiome does not appear to alter the natural course of RSV-associated pneumonia, but further study is needed to clarify the role of viral-bacterial interactions in determining outcomes in RSV lower respiratory tract infections.

### EP25-338-23 Integration of obstructive lung disease diagnostics into primary care in limited-resource settings: Is there a cost advantage?

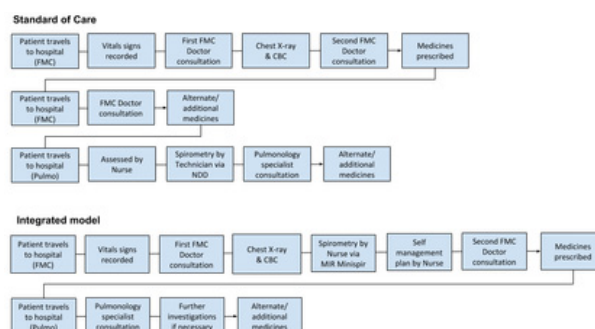
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**Background:** In Pakistan, obstructive lung diseases (OLD) are frequently managed by specialist hospital physicians. Primary care infrastructure to support the high burden of these non-communicable diseases are lacking. We compare patient and hospital costs of integrating OLD diagnosis and management systems within the family medicine clinics (FMC) at the main hospital of a free-of-cost, private health network in Pakistan, to the usual standard of care.

**Design/Methods:** OLD services were integrated into the FMC between February 2019 and 2020 with necessary capacity building and equipment. Inflation-adjusted data of the indirect and direct per-patient visit costs associated with standard care and integrated services were obtained from hospital administration between 2018 and 2020. Patient costs were assessed through a self-reported patient cost questionnaire. A cost comparison analysis was performed - assuming a 1:4 ratio of referrals from the family medicine to pulmonology specialist clinics after integration, and a 2:3 ratio prior. Patient flow process mapping was conducted to determine cycles of care and identify recurring costs.

**Results:** Total costs per patient amounted to USD29.1 for standard care and USD21.16 after service integration. After integration, direct cost savings to the patient were USD4.93. In our hospital, where 600-800 new patients

are seen in FMCs daily, a total cost saving per patient was USD3.01. Process mapping (Figure 1) demonstrated fewer steps within the patient care cycle after integration (12 steps) compared with standard care (14 steps).



[Figure 1: Process maps for standard of care and integrated care. 0 Advanced issue found]

**Conclusions:** For single-payer health systems, diagnosis and management of OLD at the primary care level may lead to lower costs for both patients and hospitals. Additional research into the cost-effectiveness of integration within both public and private health services would be useful to consider further steps in provision of OLD services in Pakistan.

### EP25-339-23 Predictive value of pulse oximetry for mortality among infants and children presenting to primary care with World Health Organization-defined pneumonia in rural Malawi

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**Background:** The mortality impact of pulse oximetry use during infant and childhood pneumonia management at the primary healthcare level in low-income countries is unknown. We sought to determine mortality outcomes of infants and children diagnosed and referred using clinical guidelines with or without pulse oximetry in Malawi.

**Design/Methods:** We matched prospectively collected community health worker (CHW) and health centre (HC) outpatient data to prospectively collected hospital and community-based mortality surveillance outcome

data, including episodes followed up to, and deaths within, 30 days of pneumonia diagnosis among children 0-59 months old. We determined differences in mortality rates using <90% and <93% oxygen saturation (SpO<sub>2</sub>) thresholds, and World Health Organization (WHO) and Malawi clinical guidelines for referral.

We used unadjusted and adjusted regression to account for interaction between SpO<sub>2</sub> threshold (pulse oximetry) and clinical guidelines, clustering by child, and CHW or HC catchment area.

**Results:** Overall 16/417 (3.8%) CHW and 13/695 (1.9%) HC episodes with outcomes died. SpO<sub>2</sub><90% and <93% identified for referral 3/13 (23%) and 4/13 (31%) HC deaths, and 1/16 (6%) CHW deaths, missed by clinical guidelines. Using chest indrawing to indicate referral at HCs identified 12/13 (92.3%) deaths. Compared to SpO<sub>2</sub>>90%, SpO<sub>2</sub><90% predicted death independently of clinical criteria: HC Risk Ratio (RR): 9.37, 95% CI: 2.17, 40.4; CHW RR: 6.85, 95% CI: 1.15, 40.9; SpO<sub>2</sub><93%, versus SpO<sub>2</sub>>93%, predicted HC-level death: RR: 6.68; 95% CI: 1.52, 29.4.

**Conclusions:** Hypoxaemic paediatric pneumonia cases identified during primary care are at high mortality risk. Primary care pulse oximetry and chest indrawing identified for referral fatal cases clinical guidelines alone missed.

### EP25-340-23 Association between fine particulate matter air pollution and emergency room visits for respiratory illnesses amongst adults in Karachi, Pakistan

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**Background:** The negative effect of air pollution on hospitalisation and emergency room visits (ERV) is well established in the literature. However, much of this literature stems from Europe, North America or South East Asia. A limited number of studies have evaluated this effect in the subcontinent, and even fewer in Pakistan.

**Design/Methods:** Fine particulate matter (PM<sub>2.5</sub>) and ERV data were retrieved from citizen air quality monitors and a free-of-cost hospital, respectively, in Karachi, Pakistan. The study analysed data from January to December 2018 utilising a Poisson regression, adjusting for potential confounders. ERV data was limited to respiratory complaints, such as asthma and shortness of breath amongst adults (age >15).

**Results:** In 2018, mean PM<sub>2.5</sub> concentrations were 38.5 µg/m<sup>3</sup> (IQR: 22.4-46.2 µg/m<sup>3</sup>), and the mean daily count of ERVs for respiratory complaints was 26.9 (IQR: 21.0-31.0). The increase in relative risk of an ERV for a respi-

ratory complaint was found to be significant (p < 0.001). Adjusting for confounders, the effect of a 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> was associated with a 2.8% increase in relative risk of an ERV. Assuming linearity, the risk of an ERV may have ranged between 6.3 and 12.9%.

**Conclusions:** Fine particulate matter air pollution was found to significantly increase the risk of an emergency room visit for respiratory complaints in Karachi, Pakistan. Further investigation into the potential impact of air pollution on health services is required as this may influence healthcare provision.

### EP25-341-23 Syndromic diagnoses and management of patients presenting to health facilities in four provinces of Vietnam

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**Background:** Respiratory diseases are common causes of presentation to healthcare facilities worldwide. In Vietnam, the clinical characteristics of patients presenting with respiratory symptoms, and the management of these patients, have not been well-characterised. We aimed to determine the prevalence of common respiratory conditions, using a standardized diagnostic approach, of patients presenting to four levels of healthcare facilities in Vietnam. We also evaluated the treatment provided to these patients.

**Design/Methods:** We conducted an observational study consisting of a baseline assessment (questionnaire, blood tests, chest x-ray, spirometry, and treatment) and a follow-up spirometry (pre- and post-bronchodilator) at four weeks. Patients ≥ 5 years presenting with dyspnoea, cough, wheezing, and/or chest tightness to health facilities in four provinces were eligible. Eight common syndromes were defined using data from the questionnaire and the tests.

**Results:** We enrolled 977 subjects from 39 facilities. The median age was 59 years (interquartile range: 47 – 67 years) and 65.8% were male. More than one in five of the cohort had fixed airflow obstruction (FAO) and 41.9% of these had associated peripheral blood eosinophilia (Table).

Reversible airflow obstruction (RAO) was seen in 2.7% of the patients. Patients meeting the criteria for upper respiratory tract infection (URTI) alone constituted



16.4% of the sample and 48.1% did not meet the criteria for any of the syndromes. Less than half of patients with FAO were given long-acting bronchodilators. A minority of patients with either RAO or FAO with eosinophilia were prescribed inhaled corticosteroids. Antibiotics were given to more than half of patients, even among those with URTI alone and none of the other syndromes.

Table. Prevalence of the syndromic diagnoses and treatment provided

Syndromic diagnosis	Prevalence		Treatment provided at all facilities						
	n (%)	95% CI	Systemic corticosteroids n (%)	Inhaled corticosteroids n (%)	Long-acting beta-agonists n (%)	Short-acting beta-agonists n (%)	Antibiotics n (%)	Anti- <i>rhinovirus</i> n (%)	Dianetics n (%)
FAO (COPD) without eosinophilia	115 (11.8)	9.8 - 13.8	47 (40.9)	30 (26.1)	48 (41.8)	17 (14.8)	75 (6.2)	0 (0.0)	5 (4.4)
FAO (COPD) with eosinophilia	83 (8.5)	6.8 - 10.2	29 (34.9)	25 (30.1)	37 (44.6)	10 (12.1)	44 (53.0)	2 (2.4)	5 (6.0)
RAO <sup>a</sup> (asthma)	26 (2.7)	1.7 - 3.7	8 (30.8)	5 (19.2)	7 (26.9)	1 (3.9)	16 (61.5)	0 (0.0)	3 (11.5)
Other airflow obstruction <sup>b</sup>	39 (4.0)	2.8 - 5.2	7 (18.0)	7 (18.0)	8 (20.5)	2 (5.1)	20 (51.3)	0 (0.0)	0 (0.0)
LRTI	82 (8.4)	6.7 - 10.1	31 (37.8)	19 (23.2)	23 (28.1)	1 (1.2)	32 (39.4)	1 (1.2)	7 (8.5)
Tuberculosis	14 (1.4)	0.7 - 2.2	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	4 (29.0)	3 (21.4)	0 (0.0)
Heart failure	46 (4.7)	3.4 - 6.0	21 (45.7)	11 (23.9)	15 (32.6)	7 (15.2)	32 (70.0)	0 (0.0)	12 (26.1)
URTI alone <sup>c</sup>	160 (16.4)	14.1 - 18.7	50 (31.3)	18 (11.3)	28 (17.5)	8 (5.0)	104 (65.0)	2 (1.3)	0 (0.0)
None of above syndromes <sup>d</sup>	470 (48.1)	45.0 - 51.2	113 (24.0)	42 (8.9)	91 (19.4)	24 (5.1)	271 (57.7)	4 (0.9)	21 (4.5)
Overall	977 (100)	-	293 (29.9)	161 (16.5)	235 (24.1)	66 (6.8)	304 (30.9)	10 (1.0)	49 (5.0)

FAO: fixed airflow obstruction; RAO: reversible airflow obstruction; COPD: chronic obstructive pulmonary disease; LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection

<sup>a</sup>Post-bronchodilator FEV1/FVC < lower limit of normal

<sup>b</sup>FEV1 increases by > 200ml and > 12% of the baseline value after inhaling short-acting beta-agonists

<sup>c</sup>Airflow obstruction on baseline spirometry without history of post-bronchodilator spirometry

<sup>d</sup>Assessed using Common Cold Questionnaire; patients with other syndromes were not included

<sup>e</sup>Includes patients without chest X-ray (342, 35%), valid baseline spirometry (104, 31.1%), or valid four-week spirometry (370, 37.9%)

[Table. Prevalence of the syndromic diagnoses and treatment provided]

**Conclusions:** This study identified a substantial dissociation between common respiratory syndromes and the treatment provided at health facilities in Vietnam. Increased access to spirometry and use of clinical treatment guidelines adapted to local settings are essential to improving patient care in Vietnam.

## EP25-342-23 Pulmonary function testing and predictive equations in child population in Mbeya, Tanzania

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**Background:** The increased use of pulmonary function testing in research as well as in diagnosing and managing of lung diseases has led to the need for locally derived reference equations in many African settings. GLI Taskforce also acknowledged that there is a lack of spirometric data for certain ethnic groups and encouraged further studies. Reference standards are widely lacking in Sub-Saharan African countries, especially for children. This study aimed at establishing lung function values and predictive equations for healthy children living in Mbeya, Tanzania.

**Design/Methods:** We applied a cross-sectional design. Eligible participants and their parents/caregivers, who provided informed consent have undergone anthropometric measurements, e.g. height, weight, answered questionnaire with demographic and behavioural components, and performed lung function testing using a

hand-held spirometer. Data were double-entered, coded and analysed using descriptive statistics and logistic regression to develop predictive equations.

**Results:** A total of 284 children produced valid spirometry results. The mean age of children was 12.5 (SD 2.2) with equal distribution of males (142) and females (142). Mean FVC in liters was 2.3 (SD 0.6) and mean FEV1 in liters was 2.0 (SD 0.5). Using GLI equations as reference standards, a total of 236 (83.1%) of children had normal lung function with the rest having abnormal ventilation pattern on spirometry – restriction (11.3%) to be the most prevalent. We constructed the predictive Tanzanian equations and compared them to GLI predictions for this age group (6.5-17.5). Associations with risk factors, e.g. passive smoking or cooking were also assessed.

**Conclusions:** To our knowledge, this was the first study to obtain local spirometric equations for children in Tanzania. The pending analyses will reveal to what extent GLI equations are appropriate for this specific African setting and what are the relevant risk factors for lung function impairment in Tanzanian children.

## EP25-343-23 Antimicrobial susceptibility patterns of Rapidly growing mycobacteria respiratory isolates: a ten-year experience in a mycobacterial research center in Colombia

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**Background:** Pulmonary infections due to Non-tuberculous Rapidly growing mycobacteria (NT-RGM) are difficult to treat, with a multidrug regimen, cure rates are between 50 to 30%. In Colombia, there is not data available about antimicrobial susceptibility patterns. The aim was to identify susceptibility patterns, determine possible changes on susceptibility profile and establish whether current guidelines are relevant for our context.

**Design/Methods:** We collected data on pulmonary NT-RGM isolates from a mycobacterial research center in Colombia, antimicrobial susceptibility testing was performed between 2010-2019 according to CLSI guidelines. Minimum inhibitory concentrations to clarithromycin, amikacin, moxifloxacin and doxycycline were recorded, linezolid and cefoxitin were added between 2017-2019. Duplicates were deleted. We determine antimicrobial susceptibility rates through the ten-year study period.

**Results:** We identify a total of 63 NT-RGM isolates, representing 47% of Non-tuberculous mycobacteria respiratory isolates. During the first period, the most frequent species was *Mycobacterium fortuitum*. During the last two periods was *Mycobacterium abscessus*, representing 50% of isolates over ten years. Susceptibility to Clarithromycin, the cornerstone of treatment for *M. abscessus* was only 60% and susceptibility was signifi-

cant lower for *M. fortuitum*. Resistance to Doxycycline was very high among isolates and moxifloxacin susceptibility was high only against *M. fortuitum*.

NT-RGM	N°	Clarithromycin	Amikacin	Moxifloxacin	Doxycycline	Linezolid	Cefoxitin
<i>M. abscessus</i>	31	61%	100%	35%	10%	60%	70%
<i>M. Fortuitum</i>	24	17%	92%	79%	17%	50%	75%
<i>M. Chelonae</i>	8	63%	88%	13%	13%	-	-

[Table.]

**Conclusions:** These results shows a different susceptibility profile among the most common NT- RGM species in Colombia. Recent guidelines (BTS) still advice doxycycline and moxifloxacin testing as main options for antimicrobial testing.

However, these drugs were partially ineffective against the majority of our isolates. Amikacin was the most effective, however, is commonly associated with severe side effects, clarithromycin susceptibility profile was lower than expected. The study evidences the need for new options to guide NT-RMG pulmonary disease treatment and provides alternative perspectives about empiric therapy.

## EP26 Improving knowledge: the benefits for person-centred TB care

### EP26-344-23 Feasibility of appreciative inquiry to co-create an evaluation framework for TB and HIV Extension for Community Healthcare Outcomes (ECHO) implementation in India and Tanzania

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**Background and challenges to implementation:** Project ECHO (Extension for Community Healthcare Outcomes) leverages video-enabled technology to promote collaborative communities of practice among ministries of health (MOH) and health care providers (HCP). ECHO democratizes knowledge, shares best practices, and promotes mentorship through guided practice and case-based learning, but no evaluation framework exists across 62 ECHO programs focusing on HIV or TB in 21 countries. We describe the feasibility of using an appreciative inquiry approach to create an evaluation framework for ECHO in India and Tanzania; both countries without baseline data/indicators to measure success.

**Intervention or response:** Appreciative inquiry (AI) is a modified strengths-based strategic thinking approach that discusses strengths and opportunities, reframes deficits and challenges through potential and possibility and forward-thinking lens. Five separate focus group discussions with 6–8 stakeholders (convenient sample by role) shared their perspectives on current status of ECHO; group reflection and feedback sessions were analyzed by themes: Strengths, Challenges, Opportunities/Aspirations, measurable Results, and Evaluation indicators (SCORE). Evaluation questionnaires included Likert scale-based questions to assess participant feedback on feasibility and acceptability of the AI approach. Fisher's exact statistics assessed associations (p-values <0.05 were considered statistically significant) between acceptability and feasibility (practicality) of the SCORE methodology among participants in India vs. Tanzania.

**Results/Impact:** Out of 64 stakeholders (India, 34; Tanzania, 30), 9 decision makers, 7 subject matter experts (SME), and 8 HCPs responded from India; 2 decision makers, 9 SMEs, and 10 HCPs responded from Tanzania (45, 70% overall response rate). Most (>81%) were satisfied with the AI workshop and felt this approach was acceptable and feasible.

There were no significant differences in evaluation results for participants between Indian and Tanzania (Table). Of note, the workshop spanned 2 days in India but only 10 hours in Tanzania.

Appreciative Inquiry workshop met or mostly met objectives (Utility):	Proportion who agreed, India (n=24)	Proportion who agreed, Tanzania (n = 21)	Fisher's exact p-value
(i) Identified measures for ECHO's successes	21 (91%)	21 (100%)	p=0.489
(ii) Revealed diverse perspectives on ECHO's strengths	23 (96%)	20 (95%)	p=1.000
(iii) Revealed diverse perspectives on ECHO's challenges	23 (96%)	20 (95%)	p=1.000
(iv) Revealed diverse perspectives on ECHO's opportunities	23 (100%)	21 (100%)	p=1.000
(v) Revealed diverse perspectives on ECHO's aspirations	21 (87%)	21 (100%)	p=0.236
Participants were satisfied or mostly satisfied with workshop (Acceptable/Feasible):			
vi) Structure and breaks	21 (87%)	19 (90%)	p=1.000
vii) Logistics (space, food, seating)	20 (83%)	21 (100%)	p=0.111
viii) Pre-workshop coordination and information	21 (87%)	17 (81%)	p=0.689

[Table.]

**Conclusions:** Appreciative inquiry was useful, acceptable, and feasible and may serve as a best practice for evaluating ECHO programs.

### EP26-345-23 Creating tuberculosis awareness through active involvement of learners in secondary schools: a case of Amref Health Africa

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**Background and challenges to implementation:** Worldwide, an estimated 1.8 million adolescents and young adults develop TB yearly, yet strategies to improve TB awareness remain minimal and underfunded. To improve this, Kenya targets to implement proactive approaches targeting audiences by age, gender and other factors and adopt innovative delivery mechanisms to improve care seeking by 2023.

**Intervention or response:** Amref Health Africa in Kenya, Brothers of St Joseph's Community Based Organization, Ministry of Health, Ministry of Education and Teachers Service Commission collaborated to create and implement activities geared towards creating TB awareness among schools, from January to March 2019. Public secondary schools in five TB high burdened counties were prioritized. Activities included; TB sensitization of county teams, school managers, nurse and/or matrons, teaching and non-teaching staff and students; distribution of Information Education Materials, creation of TB related performing arts (poems, skits, spoken word and folk songs) by students, secondary schools TB competition dubbed "Schools Tuberculosis awareness festival" and presentation and prize giving during the world TB day. Students received certificates and winning schools received 1 desk top computer, a voucher worth 50 USD to purchase TB related books and trophies. Students were guided by TB coordinators to ensure correct content is developed and presented.

**Results/Impact:** Of the targeted 249 boarding schools, 92% were visited and 141,704 students reached with TB information. 59% (134) of them participated in the competition and presented 209 items. Approximately 2900 people attended. The winners per county and 1 school for the disabled (118 students) presented in the world TB day reaching community members who attended the event. The Cabinet secretary for health directed that this should be embraced and conducted each year.

**Conclusions:** Strategies to engage the adolescents and youth in the TB agenda are necessary and should be funded adequately. Minimal resources can be used if TB is mains including.

### EP26-346-23 Integration of family-focused education and counselling in Daru TB preventive therapy program

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**Background and challenges to implementation:** Preventive therapy is recognized as a crucial step towards TB elimination and meeting the END TB global targets. However, scale up has been slow in many settings, with high lost to follow up (LTFU) rates. Daru, a small island in PNG's Western Province, is the site of an outbreak of drug-resistant TB (DR-TB). Like elsewhere in the world, community understanding of the concept of TB infection (as opposed to TB disease) in Daru has historically been low contributing to a LTFU rate for PT before intervention of 30%.

**Intervention or response:** Alongside the scale up of PT for TB household contacts <5 years of age in Daru in late 2017, a family centred education and counselling package was developed and implemented to address the lack of community understanding of latent TB infection. The package included: three standardised sessions offered in a number of languages, counselling support for issues, and home visits. Engaging tools (eg, flip charts, information handouts, visual aids) were created, tested, and implemented. Counsellors led child-friendly activities during clinics to ensure the engagement and safety of the children.

**Results/Impact:** Since initiation in October 2017 to May 2020, 1093 education and counselling sessions were provided to families by peer counsellors. The education and psychosocial support contributed to a high completion rate of 83% and drop in LTFU rate (9% from 30%).

**Conclusions:** We implemented a family-focused and child-friendly education and counselling program for children <5 years on PT and their families. This contributed to high rates of adherence and treatment completion. The lessons learnt from this program may be applied to support the scale up of PT in other parts of PNG and internationally.

### **EP26-347-23 Experience describing co-creation of an assessment framework for implementation of a virtual learning platform: Tuberculosis Extension for Community Healthcare Outcomes (TB ECHO) implementation in India**

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**Background and challenges to implementation:** Project Extension for Community Healthcare Outcomes (ECHO) is one of the virtual learning platforms utilized by India's National Strategic Plan to end TB by 2025. The National Institute for TB and Respiratory Disease (NITRD), New Delhi uses ECHO to disseminate knowledge, and promote mentorship through case-based learning to manage complex multidrug-resistant tuberculosis patients. Since November 2016, NITRD has supported 200 local TB officers and health care workers by hosting over 100 virtual ECHO sessions. Anecdotally, TB ECHO is considered successful; however, a formal monitoring and evaluation is needed to assess and sustain implementation.

**Intervention or response:** Appreciative inquiry (AI), which is a modified strengths-based, strategic planning participatory approach was used to gather a variety of perspectives on Strengths, Challenges, Opportunities/Aspirations, measurable Results, and Evaluation indicators (SCORE). A two-day workshop at NITRD included structured multiple homogeneous role-based focus group discussions (FGD) to understand the current status of ECHO, and develop data collection tools for the evaluation framework. A systematic qualitative analysis was conducted by reviewing FGD transcripts including individual quotations to identify key themes.

**Results/Impact:** Thirty-four stakeholders including 8 each, decision makers, subject matter experts or facilitators, District TB officers (DTOs), and 10 paramedical workers convened in a two-day workshop. A total of 214 quotations were assimilated into 12 themes. Perceived strengths identified were capacity building, participation, and establishing communities of practice. Perceived challenges related to administrative and logistical issues, unstable internet connectivity, and lack of engagement of leaders. Perceived opportunities/aspirations focused on developing routine monitoring and evaluation indicators, assessing public health impact, increasing session engagement and interactions, and scaling up ECHO activities. An important emergent theme recognized a potential language barrier for Hindi-speaking participants.

**Conclusions:** ECHO holds promise for capacity building and expanding partnerships. However, improving internet connectivity, and encouraging interactive discussions by facilitators during ECHO sessions may need to be prioritized to sustain success.

### **EP26-348-23 Engaging first-line care providers for screening and referral of presumptive tuberculosis (TB) patients in Nigeria: results of a targeted approach**

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**Background:** In the past, community pharmacists (CPs) and patient medicine vendors (PMVs) were engaged to identifying and referring presumptive TB clients to health facilities for further evaluation with its surrounding challenges such as delays in clients' presenting to the health facility, tracking back diagnosed patients for enrollment, losses of laboratory results.

We introduced a "hub and spoke" sample transport model to CPs and PMVs activities to address the challenges, describe the gains and losses of utilizing the hub, and spoke model and determine its effect on TB case finding.

**Design/Methods:** A retrospective review of data generated from patients and laboratory records during CPs and PMVs engagement from April 2016 to June 2019. Presumptive TB cases were identified among clients clinically screened for cough of 2 weeks duration by CPs and PMVs (spoke) across 98 LGAs in 14 states in Nigeria. Sputum was collected from presumptive cases and transported by a designated trained sample transport officer to the GeneXpert site (hub). Clients' contact details were documented, results retrieved, and outcome of diagnosis was shared with the CPs and PMVs. Linkage to treatment was done for diagnosed TB patients through referrals.

**Results:** Of 95,676 presumptive TB cases identified during the intervention period, 96.6% (n=92,430) provided sputum for TB examination. All sputa collected had documented results. Active TB was diagnosed in 8.1% (n=7,507), with 1.4% (104/7,507) being rifampicin-resistance. More than ninety percent (n=8,827) of diagnosed cases were initiated on appropriate treatment. This contributed 7.9% of all TB cases notified to the NTP in the period.

**Conclusions:** National programs should accelerate strategies towards active engagement of CPs and PMVs to expand opportunities for TB screening in communities. The use of trained staff for sputum transport and GeneXpert testing for TB diagnosis is critical for a successful CP and PMV engagement in TB prevention and control.

### EP26-349-23 Unprepared and unprotected: graduating medical students' knowledge, attitudes and practices regarding drug-resistant tuberculosis in Cape Town, South Africa

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**Background and challenges to implementation:** South Africa has a high burden of drug-resistant tuberculosis (DR-TB) and has been pioneering a decentralised management programme. DR-TB guidelines are evolving rapidly. Junior clinicians at the primary care level need to accurately diagnose, treat, and prevent DR-TB. This study aimed to determine graduating medical students' knowledge, attitudes, and practices regarding management and prevention of DR-TB.

**Intervention or response:** This is a cross-sectional study of final year medical students at the University of Cape Town, South Africa (n=240). Students were approached to complete a questionnaire designed to assess: knowledge items relating to definitions, diagnostics, and management of DR-TB; confidence in managing DR-TB

patients; perceived personal risk of DR-TB; reported practices around clinical exposure to DR-TB and use of infection control measures.

**Results/Impact:** 87 students responded (36.3% response rate). The mean knowledge score was 4.7 points (95% CI 4.42 - 5.06), out of a possible maximum of 8. Few participants (n=22, 25.3%) correctly identified the first line test used to diagnose DR-TB in South Africa. Many participants (n=74, 85.1%) reported recent contact with DR-TB patients, some avoiding contact due to fear of infection. The majority (n=80, 91.9%) acknowledged their increased relative risk of infection, with half (n=49, 55.9%) reporting personal concern of active DR-TB disease at some point during their studies, and three reporting prior TB disease. For students who develop occupational TB during their studies, psychological support (94.3%) and assistance with treatment costs (94.3%) are priorities.

**Conclusions:** DR-TB training should be incorporated into South African undergraduate programmes to equip junior clinicians to manage and prevent DR-TB. This would additionally benefit prevention strategies for other contagious occupational hazards, including novel coronavirus disease 2019. Medical students had a high level of awareness regarding personal risk of occupational DR-TB, yet still reported a significant burden of exposure and disease. Enhanced responses to attenuate occupational risk are urgently needed.

### EP26-350-23 Can patient navigators help potential TB patients navigate the diagnostic and treatment pathway?

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**Background and challenges to implementation:** People with TB symptoms face challenges in navigating the Indian health system. The onus of organising care is on the patient and their families alone. Factors like gender discrimination and opportunity cost further complicate it. Therefore, people may not complete the diagnostic and treatment pathway even if they have symptoms and experience poor health. Navigators can improve the completion of the pathway.

**Intervention or response:** We implemented two programs in India—a public sector intervention Bihar (1.02M population), and a private sector intervention in Andhra Pradesh (AP, 8.45M population). Accredited Social Health Activist (ASHA) of the public health system in Bihar and locally-employed field officers in AP facilitated patients' navigation through the health system. In Bihar, ASHA accompanied community-identified presumptive TB patients to the nearest primary health

center, assisted them through the diagnostic process and supported the patient throughout treatment after a TB diagnosis. In AP, field officers liaised with private physicians, accompanied presumptive patients through diagnosis, counselled and initiated treatment, performed contact investigation, and followed-up with patients. Both projects recorded case-based data for all the patients in a database, and used the program yield and the historical NTP notifications to evaluate the programs' effect.

**Results/Impact:** Between April 2017 and December 2018, Bihar confirmed 1730 patients, which represented an increase of 85% in public notifications compared to the baseline. 95% initiated treatment. In AP, between January 2017 and December 2018, private notifications increased with 117% compared to baseline. About 96% patients started treatment.

**Conclusions:** Patient navigators supported the patients in the diagnostic and treatment pathway and improved their health system experience. Involving navigators in TB programs may improve completion of care cascade, reducing loss to follow-up at various stages.

### EP26-351-23 A 'new normal' for health service provider capacity building in response to the COVID-19 pandemic in the Philippines

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**Background and challenges to implementation:** With the advancement in tuberculosis (TB) diagnosis and management, Philippines' National TB Control Program (NTP) revised the Manual of Procedures (MOP), which guides all TB services, and planned dissemination for nationwide implementation through face-to-face training by a pool of trainers and e-learning platforms which are under development. However, due to the COVID-19 pandemic face-to-face trainings were put on hold.

**Intervention or response:** From March to April 2020, a synchronous web-enabled class-based training for 15 pre-selected trainers and 46 other staff from several NTP development partners was conducted through eleven 3-hour sessions. The NTP endorsed training utilized available digital platforms including Microsoft Teams, Google Drive, Google Forms, and Poll Everywhere. The graduate trainers will cascade the revised NTP-MOP to the provincial NTP teams and implementers in both public and private sectors. Poll exercises with displayed answers; group question and answer sessions; and experience sharing through chat-boxes or audio devices

were adopted to enrich interaction and participation. Facilitators conducted and analyzed evaluation of each separate session and the overall training. The graduated trainers received training certificates from the NTP.

**Results/Impact:** A total of 56 participants (91.8%) completed the full training course. Pre and post-tests results of a subset of participants showed 32.9% knowledge gained. 60% of graduated trainers reported that they were very confident or confident to cascade 6 out of 11 training modules and 36% reported somewhat-confident to cascade those. 97% of the participants who responded were very satisfied with the training, overall. Qualitatively, most participants quoted that the "phase-wise or modular delivery approach allowed them to grasp and internalize what they had learned each day without overwhelming them". Variability in internet connection-strength was a challenge for some participants.

**Conclusions:** Short participant-centered interactive online training is a feasible and cost-effective "new normal" for remote capacity building for health service providers during and post COVID-19 pandemic.

### EP26-352-23 Study participants' satisfaction with directly observed therapy, and TB program staff member's interpersonal skills, patient education, and patient-centered communications

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**Background:** We conducted a randomized crossover trial comparing in-person directly observed therapy (ipDOT) with electronic DOT (eDOT) for tuberculosis (TB) treatment, in New York City TB clinics. We report measures of patient satisfaction.

**Design/Methods:** Participants took medication with each DOT method. Afterwards, participants completed a survey containing three 10-question subscales with 5-point Likert-scale response sets to rate staff members' interpersonal skills, patient education, and patient-centered communications. Replies were examined relative to participants' responses to two questions asking their satisfaction with eDOT and ipDOT.

**Results:** Of 216 persons enrolled in the trial, 132 patients received 10 or more consecutive doses of both ipDOT and eDOT. Of 132, 114 (86%) completed the questionnaire. Median age was 38 years (range: 18-86), 64% (n=73) were male, 76% (n=87) had ≥ high-school education.

Participants' satisfaction varied by DOT method: 75% (n=85) reported being satisfied with ipDOT, whereas 25% (n=29) were dissatisfied; 92% (n=105) were satisfied with eDOT compared to 8% (n=9) dissatisfied.

In their responses to the three questionnaire subscales, the median percentage of participants who rated staff members' interpersonal skills "good" "very good" or "excellent" was 97%, the median percentage reporting staff "often" or "always" provided patient education was 82%, and 85% noted staff "often" or "always" engaged in patient-centered communications.

Participants dissatisfied with ipDOT replied staff "never," "rarely," or only "sometimes" explained diagnostic testing (31%), TB medications (31%), side-effects (38%), rationale for treatment duration (34%); or involved patients in decision-making (48%). Similar responses to these five questions were provided by 11-33% of eDOT-dissatisfied, 13-21% ipDOT-satisfied, and 18-28% eDOT-satisfied participants.

35% of ipDOT-dissatisfied participants replied staff "never" or infrequently attended to participants' emotional wellbeing; while 11% eDOT-dissatisfied, 11% ipDOT-satisfied, and 17% eDOT-satisfied participants answered this way.

**Conclusions:** Perceptions of treatment-related patient education and expressions of empathy may be associated with patients' opinions of ipDOT.

### EP26-353-23 Knowledge, attitudes, and current practices and roles of pharmacy professionals concerning tuberculosis treatment in Indonesia

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**Background:** In 2014, in Indonesia, 52% of TB patients visited pharmacies prior to diagnosis. Pharmacies can be an effective channel to direct presumptive TB patients to health facilities for diagnosis and care. The study aims to investigate pharmacy professionals' knowledge, attitudes, and current practices concerning TB and the key roles that pharmacies play in the TB patient pathway.

**Design/Methods:** We conducted a cross-sectional, digital survey between December 2019 through January 2020. 418 responses were received (95% CI and 5% ME).

**Results:** Knowledge scores for TB were very low, with 38% correct answers. Those who had 0-2 hours of training had a lower median score than those who had 3 or

more hours of training (Kruskal-Wallis H test,  $\chi^2 = 15.205$ ,  $p=0.004$ ). Pharmacy professionals reported fear and nervousness (50-70%) about interacting with TB patients, with higher levels reported by females (Mann-Whitney test,  $z=-2.824$ ,  $p=0.005$ ). 87% of participating pharmacy professionals revealed that they served patients with anti-TB drug prescriptions and 93% would rather refer presumptive TB patients to a laboratory or health facility than dispense medicines without a diagnosis.

**Conclusions:** These results indicate the need for information dissemination materials and education, aiming at destigmatizing TB and ensuring that pharmacy professionals are provided adequate information on prevention, diagnosis and treatment. Furthermore, a formal referral mechanism for pharmacists to refer patients to health facilities can also decrease time to access TB treatment, increase case detection and promote health system coordination to improve TB outcomes across Indonesia.

### EP27 Difficult problems in TB infection and treatment

#### EP27-354-23 Difference in persistent tuberculosis bacteria between in vitro and sputum from patients - implications for translational predictions

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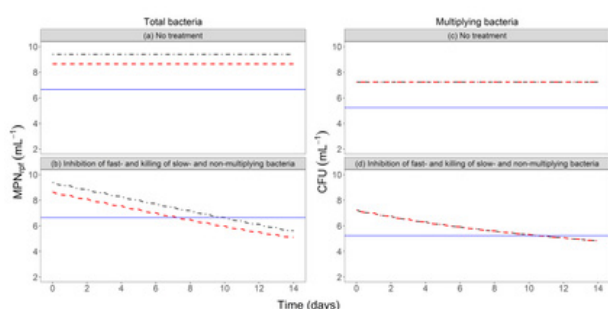
**Background:** This study aimed to investigate the number of persistent bacteria in sputum from tuberculosis (TB) patients compared to in-vitro and to suggest a model-based approach for accounting for the potential difference.

**Design/Methods:** Sputum smear positive patients (n=25) provided samples prior to onset of chemotherapy. Number of cells detected by conventional agar colony forming unit (CFU) and most probable number (MPN) with resuscitation promoting factors (rpf) supplementation were quantified. Persisters was assumed to be the difference between MPNrpf and CFU. The difference in persistent bacteria between in-vitro and human sputum before chemotherapy was quantified with a persister translational factor (PTF) using different model-based approaches with the Multistate Tuberculosis Pharmacometric (MTP) model. Simulations was performed in



an early bactericidal activity (EBA) setting to investigate the consequences of the difference in phenotypic resistance between in-vitro and human, for the prediction of drug response by CFU and MPNrpf.

**Results:** The persistent bacteria in sputum prior to chemotherapy was 17% of the in-vitro levels as predicted by the MTP model suggesting a difference in phenotypic resistance and thus total bacterial numbers (MPNrpf), whereas no difference was found for multiplying bacterial subpopulations (Figure 1). Clinical trial simulations showed that the human predicted time to 2 log fall in MPNrpf was 3 days shorter if drug response was predicted including the PTF, compared to ignoring the difference in phenotypic resistance (Figure 1).



[Figure 1.]

Predictions without the PTF (grey dot-dashed line) and with the PTF (red dashed line). The blue horizontal line illustrates the 2 log fall threshold when accounting for the PTF.

**Conclusions:** The number of persisters is lower in human compared to in-vitro, prior to chemotherapy. The discovered phenotypic differences between in-vitro and humans prior to chemotherapy have implications on translational efforts but can be accounted for using a model-based approach for translating in-vitro to human drug response.

## EP27-355-23 Characterization of the metabolic urine profile using nuclear magnetic resonance (NMR) spectroscopy to monitor treatment of tuberculosis

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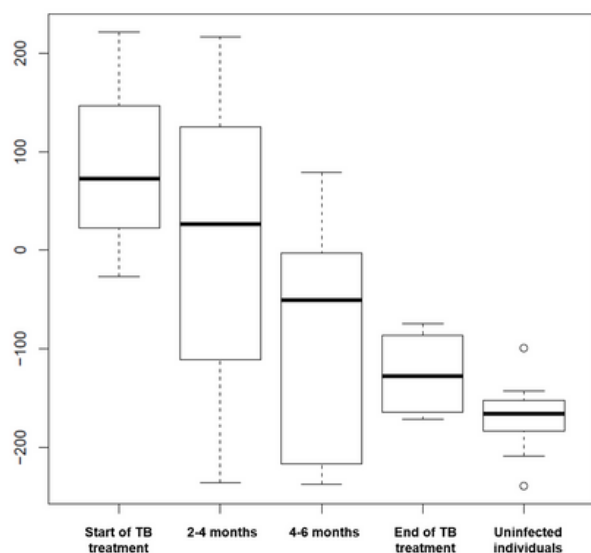
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**Background:** The emergence of drug-resistant tuberculosis (DR-TB) challenges the control of TB with an increase in treatment failure. Surveillance during treatment is essential to monitor adherence and treatment response. In this proof of concept, we aimed to characterise the urinary metabolic profile of patients receiving anti-TB treatment and its association to treatment outcome.

**Design/Methods:** We included 9 adults with drug-sensitive pulmonary TB (DS-TB) and 9 healthy controls. Patients with DST-TB received directly observed treatment for 2-month phase isoniazid, rifampicin, pyrazinamide and ethambutol and a 4-month phase of isoniazid and rifampicin. We collected urine samples at the beginning of treatment and every two months until the end of treatment. All of them were considered clinical, microbiological and radiological cured at the end of treatment.

We characterized the urinary metabolomic profile of TB patients using Nuclear Magnetic Resonance (NMR) spectroscopy. We compared the principal component analysis (PCA) scores of DS-TB patients and healthy controls.

**Results:** In the early stages of TB treatment, all patients with DS-TB showed metabolic urine profiles compatible with the disease. However, PCA scores modified over time as TB treatment progressed. At the end of treatment, patients showed a metabolomic profile similar to that of healthy controls (Figure 1). We also identified a number of exogenous metabolites related to drug-taking during TB treatment.



[Figure 1. The box plot shows the correlation between Principal Component Analysis (PCA) scores and TB treatment (in months) of TB patients and healthy controls.]

**Conclusions:** Urine metabolic profiling based on NMR of DS-TB patients can identify individuals who have received treatment and changes over the course of TB treatment. This urine metabolomic approach could be applied to monitor its correlation to individualized treatment regimens of patients with longer treatment time and poor treatment outcomes as patients treated for drug-resistant TB.

### EP27-357-23 Systemic inflammation in pregnant women with and without latent tuberculosis infection

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**Background:** Recent studies report increased systemic inflammation in adults with latent tuberculosis infection (LTBI+) compared to those without (LTBI-). However, potential differences in systemic inflammation by LTBI status has not been assessed in pregnant populations and our study objective was to address this research gap.

**Design/Methods:** We conducted a cohort study of 155 LTBI+ and 65 LTBI- pregnant women, stratified by HIV status, attending an antenatal clinic at BJ Medical College in Pune, India. Women were enrolled either in the second or third trimester of pregnancy and had their LTBI status assessed by interferon gamma release assay.

Plasma was used to measure systemic inflammation markers using immunoassays: IFN- $\beta$ , C-reactive protein (CRP),  $\alpha$ -1-acid glycoprotein (AGP), intestinal fatty acid binding protein (I-FABP), IFN $\gamma$ , IL-1 $\beta$ , soluble CD14 (sCD14), soluble CD163 (sCD163), TNF $\alpha$ , IL-6, IL-17a and IL-13. Univariable and multivariable linear regression models were fit to test the association of LTBI status with each inflammation marker.

**Results:** Study population characteristic was a median age of 23 (Interquartile range: 21-27), 28% undernourished (mid-upper arm circumference <23 cm), 25% with less than secondary education, 7% with gestational diabetes and 32% with HIV.

In multivariable models adjusting for age, mid-upper arm circumference, HIV, vegetarian diet and gestational diabetes, LTBI+ women had significantly lower levels of second trimester AGP ( $p < 0.001$ ), I-FABP ( $p = 0.03$ ), IL1 $\beta$  ( $p < 0.001$ ), IL-6 ( $p < 0.001$ ) and IL17a, and higher levels of IFN $\gamma$  ( $p = 0.02$ ) compared to LTBI- women. LTBI+ also had significantly lower levels of third trimester AGP ( $p = 0.01$ ), IL1 $\beta$  ( $p < 0.001$ ), sCD163 ( $p = 0.02$ ), IL-6 ( $p < 0.001$ ) and IL-17a ( $p < 0.001$ ).

**Conclusions:** Interestingly, LTBI+ women had lower levels of various inflammatory markers in both the second and third trimester of pregnancy compared to LTBI- women.

These findings will need to be confirmed in future studies along with further assessments on the causes and potential impact of these differences.

### EP27-359-23 Predicting the efficiency of the treatment of drug-resistant tuberculosis depending on the polymorphism variation of glutathione-S-transferase genes

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**Background:** One of the main factors of the epidemic situation control regarding drug-resistant tuberculosis is effective treatment of patients because, in addition to curing a particular case.

**Design/Methods:** A prospective, descriptive, case-control study was realized including 60 new pulmonary infiltrative drug-susceptible cases, with hepatobiliary and pancreatic comorbidities. Patients were hospitalized in the Chernivtsi Regional Clinical Phthysiopneumological Dispensary. All selected patients were microscopically positive for acid fast bacilli and were treated accord-

ing the established new case category. Polymorphism GSTM1 and GSTM1 areas were isolated using complex multi PCR for M. Arana et al (1996).

**Results:** Patients with pulmonary XDR-TB who are carriers of the wild alleles (GSTM1 + / GSTT1 +) experienced the bacterioexcretion termination more frequently with the 120th dose by 18,40%; ( $\chi^2 = 3,59$ ,  $p = 0,052$ ) and 240th doses by 45.64% ( $p=0.002$ ), respectively. With null genotype in haplotypes (GSTM1+/GSTT1 0/0, GSTT1+/GSTM1 0/0, GSTT1 0/0 / GSTM1 0/0), the frequency of bacterioexcretion at a dose of 120 was lower by 47,2 % ( $\chi^2 = 18,67$ ,  $p < 0.001$ ) with a high probability of the forecast for ineffective treatment of XDR-TB in 66.67 %.

**Conclusions:** The deletion in the promotive area of both genes (GSTT1 0/0 / GSTM1 0/0) increases the risk of no effect of antituberculosis therapy resulting from the cessation of bacterioexcretion by 16.67 times [OR = 24,50, 95% CI OR: 2,18-142 64,  $p = 0.009$ ]. The presence of mutant isoform GSTM1 genotype in haplotype (GSTT1 + / GSTM1 0 / 0) reduces the chances of effective treatment, which is the lowest with the 240th dose in XDR-TB [OR=0,07, 95% CI OR: 0,09-0,57,  $p=0,002$  and OR=0,37, 95% CI OR: 0,14-0,97,  $p=0,04$ ].

### EP27-360-23 Usefulness of gene sequencing for identification of nontuberculous mycobacteria

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**Background:** The incidence of nontuberculous mycobacteria (NTM) infection is increasing in the world. Correct identification of NTM isolates is crucial for the proper management. Currently, molecular tests (especially, line probe assay) are widely used in the clinical laboratories. However, these tests cover only the part of NTM strains and is not able to identify many of NTM species. This study aimed to evaluate the usefulness of gene sequencing for unidentified NTM isolates.

**Design/Methods:** From December 2018 to August 2019, sputum samples were culture on MGIT system and 42 NTM isolates which failed to identify species by line probe assay were collected at the Seoul Clinical Laboratories. DNA was extracted by the boiling method from liquid media. 16S rRNA gene and rpoB gene were amplified and sequenced according to CLSI guideline MM18. The sequences were analyzed using NCBI BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) and ChunLAB Truebac ID ([www.truebacid.com](http://www.truebacid.com)) databases.

**Results:** 16S rRNA sequencing provided the proper identification for seven isolates. Remaining 35 isolates showed gene amplification failure, mixed sequence, or bacteria other than mycobacteria. On the other hand, rpoB gene sequencing was able to identify 27 isolates to species level (Mycobacterium chimaera: 5, Mycobacte-

rium indicus pranii: 4, Mycobacterium intracellulare: 6, Mycobacterium kumamotoense: 1, Mycobacterium lentiflavum: 4, Mycobacterium sp. FI-13364: 2, Mycobacterium timonense: 3, Nocardia cyriacigeorgica: 1, Tsukamurella tyrosinosolvens: 1). Eight isolates not identified were subculture on Ogawa media and then sequenced again. Finally, 37 isolates (88.1%) were successfully identified.

**Conclusions:** Gene sequencing is useful as a backup method for conventional molecular test to identify NTM. Even though 16S rRNA gene sequencing is standard method for the identification of bacteria, rpoB gene is a better for NTM identification, especially when cultured with liquid culture system. Multiple gene sequencing is necessary to increase success rate.

### EP27-362-23 Latency-associated antigen Rv1733c of Mycobacterium tuberculosis improves the value of differential diagnosis of active tuberculosis and latent tuberculosis infection

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**Background:** This study aimed to evaluate the diagnostic accuracy of the Mycobacterium tuberculosis latency-associated antigens Rv1733c and Rv1733c SLP, which can induce the specific Th1 cell immune response detected by Fluorescence-Immunespot (Fluorospot), for differentiating active tuberculosis (ATB) from latent tuberculosis infection (LTBI).

**Design/Methods:** This case control study was performed at Peking Union Medical College Hospital and Beijing Chest Hospital from January to December 2017. The pathogens-confirmed ATB patients were enrolled as the case group, and those with LTBI as the control group. Fluorospot assay was used to detect the frequencies of IL-2-, IFN- $\gamma$ -secreting T cells stimulated by M. tuberculosis latency-associated antigens Rv1733c and Rv1733c SLP. Combined with ESAT-6/CFP-10-Fluorospot test, the sensitivity, specificity, predictive value and likelihood ratio of differential diagnosis of ATB and LTBI were evaluated.

**Results:** 20 pathogens-confirmed TB and 28 LTBI were included. The sensitivity and specificity of ESAT-6/CFP-10-Fluorospot for differential diagnosis of ATB and LTBI were 90% (95% CI, 68.3% to 98.77%) and 82.14% (95% CI, 63.11% to 93.94%), respectively. Af-

ter being stimulated with Rv1733c and Rv1733c SLP, the maximum AUROC was 0.711 (95% CI, 0.566-0.856) when it was drawn by the frequency of single IL-2-secreting T cells stimulated by Rv1733c SLP. With a cutoff value of 0 SFCs/2.5×10<sup>5</sup>PBMCs for frequency, sensitivity and specificity of Rv1733c SLP for differentiating ATB and LTBI were 75% (95% CI, 50.90% to 91.34%) and 60.71% (95% CI, 40.58% to 78.50%). On the basis of ESAT-6/CFP-10-Fluorospot, combined with the frequency of single IL-2-secreting T cells stimulated by Rv1733c SLP, the sensitivity and specificity were increased to 100% (95% CI, 83.16% to 100.00%) in parallel testing and 92.86% (95% CI, 71.77% to 97.73%) in serial testing respectively.

**Conclusions:** Rv1733c SLP can be used as an alternative antigen for T cell-based tuberculosis diagnostic tests, in combination with ESAT-6 and CFP-10, to conductive differentiate between ATB and LTBI.

	Sensitivity (95%CI)	Specificity (95%CI)	PLR (95%CI)	NLR (95%CI)	PPV (95%CI)	NPV (95%CI)
Frequencies of single IFN- $\gamma$ -secreting T cells stimulated by EAST-6 / CFP-10	70.00 (45.72–88.11)	64.29 (44.07–81.36)	1.96 (1.10–3.48)	0.47 (0.23–0.96)	58.33 (36.64–77.89)	75.00 (53.29–90.23)
Proportion of single IFN- $\gamma$ -secreting T cells stimulated by EAST-6 / CFP-10	85.00 (62.11–96.79)	71.43 (51.33–86.78)	2.98 (1.61–5.50)	0.21 (0.07–0.61)	68.00 (46.50–85.05)	86.96 (66.41–97.22)
Frequencies of single IL-2-secreting T cells stimulated by Rv1733c SLP	75.00 (50.90–91.34)	60.71 (40.58–78.50)	1.91 (1.13–3.23)	0.41 (0.18–0.93)	57.60 (36.02–76.65)	77.27 (54.63–92.18)
Parallel test (EAST-6 / CFP-10)	90.00 (68.30–98.77)	57.14 (37.18–75.54)	2.10 (1.34–3.30)	0.17 (0.05–0.68)	60.00 (40.60–77.34)	88.89 (65.29–98.62)
Serial test (EAST-6 / CFP-10)	65.00 (40.78–84.61)	82.14 (63.11–93.94)	3.64 (1.54–8.58)	0.43 (0.23–0.79)	72.22 (46.52–90.31)	76.67 (57.72–90.07)
Parallel test (EAST-6 / CFP-10 / Rv1733c SLP)	100.00 (83.16–100.00)	35.71 (18.64–55.93)	1.56 (1.18–2.05)	0	52.63 (35.82–69.02)	100.00 (69.15–100.00)
Serial test (EAST-6 / CFP-10 / Rv1733c SLP)	45.00 (23.06–68.47)	92.86 (76.50–99.12)	6.30 (1.52–26.08)	0.59 (0.39–0.89)	81.82 (48.22–97.72)	70.27 (53.02–84.13)

[Table.]

## EP27-363-23 Dried blood spot sampling to assess rifampicin pharmacokinetics among tuberculosis patients in Paraguay: native indigenous and general population

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**Background:** In a move towards individualized tuberculosis (TB) treatment, a minimally invasive alternative sampling matrix such as dried blood spot (DBS) has gained significant attention for its advantages over venous blood sampling. DBS samples collected utilizing limited sampling strategy (two- to three- sampling time points for estimation of PK parameters) is changing the landscape of traditional therapeutic drug monitoring.

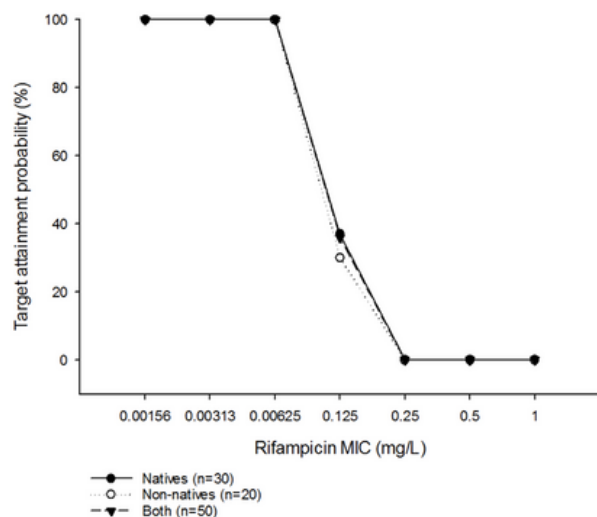
The aim of this study was to evaluate the difference in pharmacokinetics of rifampicin in native indigenous versus non-native Paraguayans using DBS sampling.

**Design/Methods:** This was a prospective pharmacokinetic study that enrolled hospitalized TB patients receiving oral rifampicin (450-600 mg once daily dosing) in Paraguay. Steady state dried blood spots samples were collected at 1, 4, and 6 hours after rifampicin intake. Rifampicin concentrations were quantified using liquid chromatography- tandem mass spectrometry. Area under the time concentration curve 0-24hrs (AUC<sub>0-24</sub>) were calculated using a validated population PK model (MW/Pharm++, Mediware). Rifampicin AUC<sub>0-24</sub> <38.7 mg\*h/L were considered as low. Probability of target attainment (PTA) was calculated using AUC<sub>0-24</sub> / MIC >271 as a target and estimated MIC values of 0.125 and 0.25 mg/L.

**Results:** In total 50 patients were included receiving 10 mg/kg once daily. Indigenous patients (n=30) showed comparable exposure as the general population (n=20) (median AUC<sub>0-24</sub> 26.8 (18.9-42.7 IQR) and 28.0 (22.2-35.3 IQR) (p=0.804).

Among total patients (n=50), only 22% had a rifampicin reference AUC<sub>0-24</sub> > 38.7 mg\*h/L.

Furthermore, PTA analysis (n=50) showed that only 36% of patients met target AUC<sub>0-24</sub> / MIC >271 (MIC assumed at 0.125 mg/L) which plummeted to 0% at a median wild type MIC of 0.25 mg/L (Figure 1).



[Figure 1.]

**Conclusions:** Considerably higher doses of rifampicin will be needed to attain target exposure in both groups. We successfully used DBS and limited sampling for AUC<sub>0-24</sub> estimation. A prospective trial using higher dosages of rifampicin supported by DBS is required before implementation in routine care.

## EP28 Making the most of short money to fight TB

### EP28-364-23 Examining the cost of delivering TB prevention, diagnosis and treatment in the Philippines, 2018

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**Background:** Philippines's government aims to accelerate TB reduction through the provision of universally accessible and affordable quality services in Philippines. This study aimed to estimate costs of delivering TB services, previously unavailable.

**Design/Methods:** Data was collected from a multi-stage stratified random sampling of 28 facilities including 39% private in 3 regions in the Philippines. Per facility, data

were collected on TB services delivered following global standards and tools. Collection for top-down (TD) and bottom-up (BU) facility-level unit cost estimates included TB service statistics, space, equipment, staff time (including observation and interviews or time-sheets), drugs and supplies, transport and other recurrent costs. Annualized economic costs are reported in 2018 dollars.

**Results:** Mean cost to deliver interventions per patient were obtained BU and TD. BCG vaccination for children was US\$3.47 (BU) and US\$5.01 (TD).

TB prevention with 6 months-isoniazid in public facilities, was US\$28 for children below five and US\$44 including US\$29 (BU) in drugs for HIV positive adults.

Intensified case finding was more costly for HIV positive with pulmonary TB (PTB) (US\$5.82, BU) than extra-pulmonary TB (EPTB) patients (US\$4.73, BU). Cough triage for PTB attending public facilities costs US\$4.32 (BU).

First line treatment per PTB adult ranges from US\$173 including US\$41 for drugs (BU) for new, to US\$427 including US\$88 for drugs (BU) for previously treated cases and per new PTB child (BU) US\$150.

Second line treatment delivered through outpatient care model in public facilities had a cost averaging for short regimen (adults only) US\$1902 including US\$712 (BU) for drugs and for long regimen US\$5000 in adults including \$2379 (BU) for drugs; and US\$3508 in children including US\$1313 (BU) for drugs.

**Conclusions:** TB service delivery packages and their cost at the facility level may now inform the fine-tuning resource allocation and health insurance package design in the Philippines.

### EP28-365-23 Examining the cost of delivering TB prevention, diagnosis and treatment in India, 2018

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**Background:** The economic analysis required to support increased investment in tuberculosis is in its infancy in India. The objective of this work was to estimate the costs of tuberculosis services from a health systems' perspective to enable India's National Tuberculosis Elimination Programme (NTEP) allocate their resources in an efficient way.

**Design/Methods:** Data was collected from a multi-stage stratified random sampling of 20 facilities delivering tuberculosis services in two purposively selected states in



India. Data were collected on tuberculosis services delivered following Global Health Cost Consortium standards, tuberculosis costing methods and Value TB data collection and analysis tools. Components for top-down (TD) and bottom-up (BU) estimates included facility characteristics, tuberculosis service statistics, building space, equipment, staff time, drugs and supplies, training, transport and other recurrent costs. Annualized economic costs are reported in 2018 US dollars.

**Results:** Cost to deliver three interventions and 49 tuberculosis services varied by costing method, facility level, and ownership. Average BU BCG vaccination cost was US\$0.77 mostly implemented in public setting. Passive case finding, defined as one screening visit, had an average BU cost of US\$1.57. Complete first-line treatment administered only in public facilities, had a mean BU cost for new pulmonary cases US\$80 including US\$54 for drugs and for extra-pulmonary US\$75 including US\$54 for drugs. For previously treated cases, BU cost averaged US\$140 including US\$92 for drugs for pulmonary and US\$128 for extra-pulmonary including US\$84 for drugs. Higher cost for pulmonary cases was attributable to follow-up laboratory tests during and end of treatment. Included in 49 TB services, average BU costs for sputum smear microscopy, Xpert, digital x-ray were US\$2.38, US\$15 US\$2.74 respectively.

**Conclusions:** Unit cost information from this study can be used for estimating the investments required for implementing the revised algorithm for diagnosis and treatment of tuberculosis patients, as inputs in modelling exercise and in economic evaluations.

### EP28-366-23 First national TB patient cost survey in Lao PDR: assessment of the financial burden faced by TB-affected households and comparisons by drug-susceptibility and HIV status

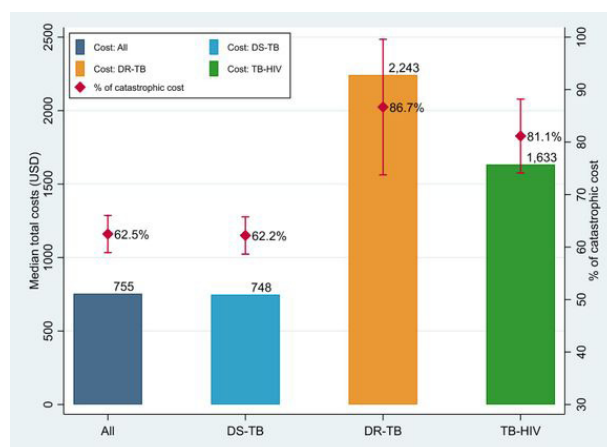
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**Background:** TB patients incur large costs for care seeking, diagnosis, and treatment. To understand the magnitude of the financial burden and its main cost drivers, Lao PDR National TB Programme carried out the first national TB patient cost survey in 2018-2019.

**Design/Methods:** A facility-based cross-sectional survey was conducted on nationally representative samples of TB patient at public health facilities across 12 provinces. A total of 848 TB patients were interviewed using a standardised questionnaire developed by WHO. Infor-

mation on direct medical, direct non-medical costs, and indirect costs as well as household income and coping mechanism were collected.

We estimated the percentage of TB-affected household facing catastrophic costs which was defined as total TB-related costs accounting for more than 20% of annual household income.



[Figure.]

**Results:** Of all participants, 62.5% of TB-affected households faced catastrophic costs. The proportions were much higher among households with DR-TB patients (84.8%) and TB-HIV coinfecting patients (81.0%). The median of total costs was US\$ 755 [IQR 351-1,454]. The total costs were driven by direct non-medical costs (46.6%) and income loss (37.6%). Nutritional supplements other than regular diet accounted for 74.7% of non-medical costs. A half of patients used savings, borrowed money or sold household assets to cope with TB. The proportion of patients who were unemployed increased from 16.8% to 35.4% during the TB episode especially among those who were working in the informal sector.

**Conclusions:** In Lao PDR, TB patients and their households faced substantial financial burden due to TB despite free TB services available in public health facilities. As non-medical and indirect costs were major cost drivers for TB, providing free TB services only is not enough to ease patient financial burden. Expansion of existing social protection schemes and interventions to improve access to quality TB diagnostic services are necessary.

### EP28-367-23 Economic evaluation of patient costs associated with TB diagnosis and care in Papua New Guinea

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**Background:** Costs associated with tuberculosis (TB) diagnosis and care can affect patients' adherence to treatment, leading to poor outcomes and an increased risk of TB transmission. To evaluate the magnitude and main drivers of these costs, the World Health Organization (WHO) recommends undertaking periodic TB patient cost surveys.

**Design/Methods:** We conducted the first national TB patient cost survey in Papua New Guinea to evaluate costs associated with TB disease using WHO-recommended methodology. TB patients of all ages and all types of TB were interviewed between May 2018–April 2019 at 40 facilities selected by probability proportional to size. Catastrophic costs were defined as total out-of-pocket direct and indirect costs experienced by TB-affected households exceeding 20% of annual household income. Data were analysed using descriptive statistics and logistic regression.

**Results:** Of the 1000 survey participants, 19 (1.9%) had drug-resistant TB (DR-TB). Overall, 420 (42.0%) TB patients/households experienced catastrophic costs due to TB disease; the burden was higher for those with DR-TB (79.0%). Hospitalization during TB treatment (adjusted odds ratio [aOR]=2.46; 95% CI:1.66-3.65), being in the poorest wealth tertial (aOR=5.37; 95% CI:3.66-7.90), and being employed before contracting TB (aOR=2.37; 95% CI:1.66-3.37) were independently associated with an increased risk of catastrophic costs. Most TB costs were indirect (55.3%) referring to lost wages and income during TB care-seeking and treatment. Only 3.3% of TB patients had health insurance, and 26.4% took out a loan or sold assets to finance TB care; 23.0% of patients lost employment due to TB.

**Conclusions:** The costs of TB care are catastrophic for a large proportion of patients in Papua New Guinea, and most of the costs are caused by loss of income during the illness. Mitigating indirect costs and expanding access to TB care could reduce economic burden of the disease to TB patients and their households.

### EP28-368-23 Catastrophic costs for TB patients before treatment starts – results from a multi-country observational cohort study in sub-Saharan Africa

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**Background:** Persons with tuberculosis (TB) often incur substantial costs in accessing health care. We determine the proportion facing catastrophic total costs, defined as total direct and indirect medical costs exceeding 20% of annual household income, prior to TB treatment initiation.

**Design/Methods:** Ongoing observational cohort study among patients receiving treatment for TB through national TB programs in four high TB burden countries. Adults ( $\geq 18$  years) with drug-susceptible TB were recruited at TB treatment initiation between 09/2017-02/2020. An adapted version of the WHO TB Patient Cost Survey instrument was used at enrolment to capture direct (medical and non-medical) and indirect costs (loss of income); individual and household income' and coping strategies adopted in the period prior to treatment initiation. We report median costs from the patient perspective and the proportion facing catastrophic costs, stratified by country and approach, in 2018 USD.

**Results:** 1360 patients were analysed. Costs varied widely by country (Table 1), from very modest in South Africa to substantial in The Gambia. Loss of income was contingent on the duration between onset of symptoms and initiating treatment (median 32 days IQR: 21-84). The proportion of facing catastrophic costs ranged from 10.5% to 54.0% across countries. The proportion of patients using dissaving strategies (borrowed money, sold property, or used savings) to cope with TB ranged from 1% to 50%. As a result, large proportions in each country self-reported that TB had a "serious or very



serious” impact on their financial status: 83 (20%) in Mozambique; 39 (11%) in South Africa; 198 (57%) in Tanzania; and 354 (26%) in The Gambia.

Country (per capita GDP 2018) and N	Median days from symptom onset to start of TB treatment	Median (IQR) costs/patient in USD <sup>1</sup>			Pre-treatment total costs	Catastrophic total costs by approach (n, %)			
		Pre-treatment direct medical costs**	Pre-treatment direct non-medical costs**	Pre-treatment indirect costs**		Costs >20% reported household income <sup>3</sup>	Used savings/ Borrowed money	Sold property	
Mozambique (549) n=386	28 (21-56)	\$0.40 (0.10-5.80)	\$0.30 (0.00-0.70)	\$0.00 (0.00-58.50)	\$10.45 (0.77-83.60)	11/105 (10.5%)	145 (84.7%)	49 (11.7%)	7 (1.7%)
South Africa (56374) n=343	25 (14-28)	\$0.00 (0.00-5.60)	\$2.20 (0.00-5.40)	\$0.00 (0.00-14.90)	\$8.48 (1.79-67.70)	40/284 (14.1%)	22 (6.2%)	20 (5.6%)	2 (0.6%)
Tanzania (51951) n=277	56 (29-112)	\$8.80 (3.50-21.40)	\$1.20 (0.39-3.20)	\$45.00 (0.00-140.00)	\$70.72 (24.00-382.40)	95/176 (54.0%)	77 (22.1%)	82 (23.6%)	59 (16.9%)
The Gambia (5716) n=354	56 (28-84)	\$9.50 (3.80-20.00)	\$2.20 (1.20-4.40)	\$60.70 (0.00-253.20)	\$83.90 (14.24-288.02)	13/52 (25.0%)	179 (50.1%)	28 (7.8%)	25 (7.0%)

<sup>1</sup>Approach #1: Catastrophic costs defined as total pre-treatment direct and indirect medical costs exceeding 20% of annual pre-treatment household income, among those who reported pre-treatment direct and indirect medical costs and pre-treatment household income. Household income prior to symptom onset (6 months prior to treatment initiation) was used as the denominator for catastrophic total costs. Household income was obtained from patient self-report of the exact amount or identified from prompted income ranges.

<sup>2</sup>Approach #2: Participants were asked about their use of several coping strategies to meet the costs of TB, including using savings, selling assets, borrowing money, or selling property and also whether they had suffered serious financial strain.

<sup>3</sup>Direct medical costs include consultations, medication, laboratory tests, procedures etc. Direct non-medical include food, accommodation, transport etc. Indirect costs are the self-reported income loss, defined as any loss in income during the period from symptom onset to start of TB treatment.

<sup>4</sup>All costs reported in United States Dollar (USD) (2018 annual average).

[Table 1. Estimates of catastrophic costs by country and approach (N=1360)]

**Conclusions:** Even before starting treatment, TB-related costs have a substantial impact on individuals’ and households’ financial welfare. Those experiencing catastrophic costs prior to treatment initiation are likely more vulnerable to financial hardship during and after treatment, which may in turn harm treatment outcomes and long-term recovery.

### EP28-369-23 Financial risk protection benefits of expanded TB control interventions in Ethiopia: an extended cost-effectiveness analysis modelling study

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**Background and challenges to implementation:** Tuberculosis (TB) is a large public health problem worldwide. The economic burden of seeking TB care is high and places people at high risk of financial hardship. The World Health Organization’s End TB Strategy has a target that no TB-affected households face catastrophic TB costs by 2020 and later. We assessed the impact of enhanced TB control on reducing TB-related catastrophic costs in Ethiopia.

**Intervention or response:** Three TB control strategies were investigated: active case finding, enhancing DOTS implementation for drug susceptible TB, and improvement in drug resistant TB care. Using TIME modelled TB incidence, mortality, and cost borne by patients; we projected reductions in TB-associated catastrophic costs due to implementation of those interventions between 2018-2035. TB-related catastrophic costs were defined as total costs (direct and indirect) exceeding a 20% of household annual income. Intervention effects were quantified by quintiles as changes in the number of households incurring catastrophic costs relative to the baseline. Data analyses were carried out using R Studio (version 3.6.1).

**Results/Impact:** Active case finding could reduce catastrophic costs associated with TB by 35% in Ethiopia over 2018-35; enhancing DOTS for drug susceptible TB

would avert 15% of all catastrophic costs; and improvements in multidrug-resistant TB care would avert up to 6% of all catastrophic costs of the base case. The benefits would be greatest for the poorest two income quintiles.

**Conclusions:** Improvement in the delivery of TB services may reduce substantially the catastrophic cost burden on affected households. In addition to the effective provision of healthcare services, there is a need to ensure that TB patients and affected households are given adequate financial protection measures.

### EP28-370-23 Cost-effectiveness of nutritional supplementation to decrease tuberculosis incidence and mortality in India

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**Background:** At least one in three tuberculosis (TB) cases in India are attributable to undernutrition. Undernutrition also increases risk for TB-associated mortality. An estimated 195 million Indians face food insecurity. Addressing undernutrition is therefore crucial to achieve the Indian government’s aim of eliminating TB by 2025. Independent of TB, undernutrition decreases quality of life and economic productivity. A government-run targeted public distribution system (TPDS) provides food rations to impoverished Indian households. Our aim was to assess the cost-effectiveness of providing augmented rations through TPDS to undernourished Indians to prevent TB cases and deaths.

**Design/Methods:** Through a Markov cohort model, we simulated disease progression and mortality to assess cost-effectiveness of augmented rations. The model calculates costs and outcomes (quality-adjusted life years, QALYs) associated with an enhanced 2600 KCal/day diet. Patients were stratified by their risk for TB disease: general population, household contacts (HHC) of persons living with TB, and persons living with HIV (PLHIV). The augmented rations strategy was compared to a “do nothing” scenario wherein usual TPDS rations were unchanged. Model robustness was assessed using deterministic and probabilistic sensitivity analyses. Willingness to Pay was set at \$1980, India’s per-capita gross domestic product.

**Results:** Over 5 years, nutritional supplementation could avert 0.6%, 2.8% and 4.6% of TB cases and prevent 0.1%, 0.5%, 0.9% of TB deaths in the general population, HHC, and PLHIV models, respectively. Base-case analyses found that in the general population augmented rations was highly cost-effective (ICER: \$1081.2/QALY). ICER was lower for HHCs (\$1044.5/QALY) and PLHIV (\$1007.4/QALY). Most of the utility was accrued from

positive externalities of mitigating undernutrition. The model was sensitive to the utility weight of undernutrition and cost of augmented rations.

Strategy	Cost	ICER	TB disease	TB death	Resolution of undernutrition
<b>General Model</b>					
Usual Care	2.87		1.26%	0.21%	9.41%
Augmented rations	622.05	1081.22	0.63%	0.09%	67.60%
<b>HHC Model</b>					
Usual Care	12.09		5.30%	0.90%	9.38%
Augmented rations	627.37	1044.53	2.49%	0.36%	67.57%
<b>PLHIV Model</b>					
Usual Care	38.46		16.90%	2.03%	9.33%
Augmented rations	546.78	1007.42	12.26%	1.14%	67.25%

[Table.]

**Conclusions:** Our analysis shows that augmented rations through TPDS is cost-effective compared to usual rations considering international costs per QALY thresholds.

### EP28-371-23 Modeling the impact of a bedaquiline-containing short-course regimen on cost and disease burden of drug-resistant tuberculosis in the Philippines

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**Background and challenges to implementation:** To assess the impact on disease burden and healthcare costs in the Philippines of the WHO-recommended bedaquiline-containing short-course regimen (SCR) for drug-resistant tuberculosis (DR-TB).

**Intervention or response:** A disease state transition model incorporating three TB states (susceptible, latent and active), and both drug-sensitive and DR-TB patients, was developed and calibrated to published historical metrics of disease burden (incidence, prevalence). Healthcare costs (hospitalization, drugs, other medical and out-of-pocket) were evaluated. The DR-TB SCR was considered to be used in 90% of patients from 2020. The model was used to estimate disease burden and healthcare costs in 2 scenarios – 1) the baseline, with minimal bedaquiline adoption in SCR and 2) widespread adoption of the bedaquiline-containing SCR (peak share of 90% by 2021). The treatment success rate for bedaquiline-containing SCR was taken to be 80%, versus 58% for the established injectable-containing reg-

imens. The cost-effectiveness of scenario-2 versus scenario-1 was analyzed by taking into account both direct healthcare and indirect costs, and factoring in disability-adjusted life-years (DALYs).

**Results/Impact:** Over 2020-2040, overall DR-TB healthcare costs in the Philippines have been estimated to be \$3.7B and \$2.4B (-35%) for scenarios 1 and 2 respectively, costs per treated patient were \$5.6k and \$4.3k (-25%) respectively, and costs per successfully-treated patient were \$10.7k and \$6.1k (-43%) respectively. The expected cumulative annual incidence of DR-TB over this period is estimated to be 523.8k and 500.4k (-5%) in the 2 scenarios respectively. In the cost-effectiveness analysis, scenario-2 was found to be dominant, with \$1.7B (34%) saved in costs and 1.9M (13%) DALYs averted over 2020-2040, versus scenario-1.

**Conclusions:** An optimal implementation of bedaquiline-containing regimens in the short-course regimen in the Philippines significantly reduces DR-TB disease burden by successfully treating more patients and reduces overall healthcare cost and the cost per successfully treated patient. These factors compel broader inclusion of bedaquiline in the short-course DR-TB treatment.

### EP28-372-23 The potential value of biomarker-led preventive therapy in eliminating TB: a modelling analysis

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**Background:** Novel biomarker signatures offer prognostic value in identifying individuals at imminent risk of developing active TB ('incipient' TB), and thus in identifying who would benefit most from preventive therapy. Could such tools offer cost-effective approaches for TB control in high-burden settings? We addressed this question in the context of an urban setting in India.

**Design/Methods:** We developed a mathematical model of TB transmission in Chennai, India. We investigated two screening strategies: slum-targeted (slums only) and untargeted (slum and non-slums alike). For the performance of a hypothetical biomarker test, we drew from WHO target product profiles (TPP) published in 2017. We incorporated a simple cost model for programmatic spending on TB services, as well as on the implementation of the biomarker test.

**Results:** A test meeting the TPP would avert 20% (95% CrI 12-34%) and 11% (95% CrI 6-18%) of cumulative TB incidence between 2020-2035 compared to the status quo, under targeted and untargeted scenarios, respectively, if 25% of the population is screened per year. The cost of screening is likely to be the dominant cost-driver. This is because, to detect one case of incipient-TB, 92 (95% CrI 39-164) individuals will need to be screened, under an untargeted strategy. This decreases

to 68 (95% CrI 29-117) under a targeted strategy. Even in the latter scenario, the cost-per-test will need to be less than US\$1 per person, regardless of test performance, screening rate or screening strategy, in order to be cost-effective.

**Conclusions:** Biomarker-led preventive therapy can have a meaningful impact on TB incidence in urban settings in India. However, the cost of implementing such a strategy is driven by the large numbers of people needing to be screened, in order to identify those needing preventive therapy, even in a high-risk population. Our results suggest that their cost-effectiveness would need to be carefully considered.

### EP28-373-23 Do evaluations of Tuberculosis Active Case Finding report estimates of resource need? A review of the evidence

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**Background:** Tuberculosis active case finding (ACF) interventions aim to improve early TB case detection and reduce transmission of infection. ACF has attracted significant funding, despite considerable uncertainty in resource need and cost-effectiveness measures, which are essential for the efficient allocation of limited country budgets. We aim to describe the level of resource needs reported in evaluations of ACF.

**Design/Methods:** We identified published ACF intervention evaluations from a previous systematic review. From these we collated information on the reported resource needs.

We recorded information on the:

- (i) diagnostic algorithm,
- (ii) number of tests performed per diagnostic step in the algorithm,
- (iii) human resource requirement,
- (iv) human resource investment (training) and;
- (v) auxiliary resource requirements.

We categorised evaluations into those with a 'Minimum' (i-ii), 'Intermediate' (i-iv) or 'Maximum' (i-v) availability of resource needs data.

**Results:** Data were obtained from 65 evaluations. 38% [25/65], 11% [7/65] and 3% [2/65] had Minimum, Intermediate or Maximum reporting of resource needs data, respectively. 25% [16/65] had insufficient information available to calculate any resource need. Evaluations from the African (52% [12/23]) and Western Pacific (44% [7/16]) regions contained the most resource needs data.

**Conclusions:** Existing evaluations do contain useful information that could be used for resource allocation decision-making at country level, but are likely to un-

derestimate resource needs. We advocate for more extensive reporting of resource needs in future TB intervention evaluations, and further work to make resource need data available in other areas of TB care and prevention.

### EP28-374-23 Estimating the value-based price of new tuberculosis vaccines in India and China

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**Background:** New tuberculosis (TB) vaccines have made substantial progress within the vaccine development pipeline. However, the emergent epidemic of rifampicin resistant and multidrug resistant tuberculosis (RR/MDR-TB) threatens global TB control efforts. Estimating the value of new TB vaccines must include costs to national TB programmes (including RR/MDR-TB costs) and vaccine-related costs. We estimate the value-based price (VBP) of new TB vaccines, incorporating all related costs.

**Design/Methods:** We constructed a drug-resistance stratified dynamic transmission model of TB and RR/MDR-TB, set in China and India over 1950–2050. In 2027, we simulated a 50% efficacy, post-infection efficacy, prevention of disease TB vaccine conferring 10 years of protection, administered routinely to 9-year olds and through mass campaigns to  $\geq 10$ -year olds.

We sampled TB-related and vaccine-related costs from uncertainty ranges derived from country data. We estimated the value-based price (VBP) of vaccines over 2027–2050, incorporating the direct and indirect (transmission) epidemiologic impact of TB vaccine into this cost-model.

We estimated VBP at three country-specific willingness-to-pay thresholds (2018US\$): 1-times GDP per capita, and upper and lower healthcare opportunity cost based thresholds. In India we used thresholds of US\$2016, US\$363 and US\$264. In China, we used thresholds of US\$9771, US\$5669 and US\$3560.

**Results:** Vaccination averted more TB deaths in India than China from 2027-2050 (not shown). We found higher VBP estimates in India than China for all 3 thresholds. VBP estimates are summarised in Table 1.

Table 1: Value Based Price of TB vaccine Estimates-China and India for a 50% efficacy post-infection vaccine conferring 10-years of protection. Costs and benefits discounted at 3%.GDP per World Bank 2018. Values expressed in US\$. UI: uncertainty interval.

Country	Value Based Price (USD\$)		
	1 times GDP	HCOC (upper)	HCOC (lower)
China	16.3 (11.8–21.0)	8.5 (5.9–11.3)	4.5 (2.8–6.3)
India	67.9 (59.2–77.0)	13.4 (11.5–15.4)	10.1 (8.7–11.7)

[Table.]

**Conclusions:** Vaccines averted more TB mortality in India than China. Despite lower TB-related costs, we found higher VBP estimates in India than China.

Our model also suggests that the TB response in Mozambique is not likely to meet the 2035 End-TB targets and more TB funding is needed.

**Conclusions:** Increasing investments in active case finding programs are essential to improve the estimated case detection rate of 52% - a key breakpoint in the TB cascade. In addition, a revised target or timeline and more funding for the TB program are needed.

### EP28-375-23 Optimizing investments in Mozambique's tuberculosis response: results of a TB optima modeling study

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**Background and challenges to implementation:** Mozambique is one of the 30 highest tuberculosis (TB) burden countries in the world with an estimated 551 new TB cases per 100,000 population, a low TB detection rate of just above 50%, and a low DR-TB diagnosis and treatment success rate (38%). Overall, historical data from the National Tuberculosis Programme shows an increasing trend in TB case detection rate (36% in year 2010 to 53% in 2017) coupled with a high treatment success rate for drug susceptible tuberculosis (90%). However, it is still far from the NTP targets for 2025 as well as End-TB targets for 2035. We conduct mathematical analyses to project future trends of the TB epidemic and determine which TB programming activities should be prioritized.

**Intervention or response:** To carry out the analyses, the team used Optima TB, a mathematical model of TB transmission and disease progression integrated with an economic and program analysis framework.

**Results/Impact:** Our model indicates a declining future trend in TB incidence, TB prevalence and TB-related deaths (rates). Furthermore, Mozambique can cut TB prevalence and TB deaths by 20%, and TB incidence by 11% by allocating resources optimally. Specifically, this can be done by

- (i) doubling the rate of household contact tracing for notified cases,
- (ii) screening all PLHIV during their routine outpatient visits, and
- (iii) focusing on the community outreach activities among key populations such as prisoners, cross-border miners and community health workers.

## ABSTRACT PRESENTATIONS SATURDAY 24 OCTOBER 2020

### ORAL ABSTRACT SESSION (OA)

#### OA-32 Reaching the most vulnerable

##### OA-32-694-24 The positive externalities of migrant-based tuberculosis control strategy in a Chinese urban population with internal migration: a transmission-dynamic modelling study

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**Background:** Large-scale rural-to-urban migration has changed the epidemiology of tuberculosis in large Chinese cities. We estimated the contribution of tuberculosis importation, reactivation of latent infection, and local transmission to new Tuberculosis (TB) cases in Shanghai, and compared the potential impact of intervention options.

**Design/Methods:** We developed a transmission dynamic model of tuberculosis for Songjiang District, Shanghai, which has experienced high migration over the past 25 years. We calibrated the model to local demographic data, TB notifications, and molecular epidemiologic studies.

We estimated epidemiological drivers as well as future outcomes of current tuberculosis policies and compared this base-case scenario with scenarios describing additional targeted interventions focusing on migrants or vulnerable residents.

**Results:** The model captured key demographic and epidemiological features of tuberculosis among migrant and resident populations in Songjiang District, Shanghai. Between 2020 and 2035, we estimate that over 60% of tuberculosis cases will occur among migrants and that approximately 43% of these cases will result from recent infection. While tuberculosis incidence will decline under current policies, we estimate that additional

interventions—including active screening and preventive treatment for migrants—could reduce tuberculosis incidence by an additional 20% by 2035.

**Conclusions:** Migrant-focused tuberculosis interventions could produce meaningful health benefits for migrants, as well as for young residents who receive indirect protection as a result of reduced tuberculosis transmission in Shanghai. Further studies to measure cost-effectiveness are needed to evaluate the feasibility of these interventions in Shanghai and similar urban centers experiencing high migration volumes.

##### OA-32-695-24 TB WGS and MIRU-VNTR analysis in the main foreign-born groups and among Dutch: high transmission in 2nd generation and pre- and post-entry in asylumseekers

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**Background:** In low-incidence countries such as the Netherlands, the main burden of tuberculosis (TB) is in immigrants. TB control policy consists of screening for active TB upon immigration and contact investigation after detection of a TB case. Most latent TB infections (LTBI) are found and treated in the context of contact investigation, screening for travel/work, or immune suppression. In view of the target of TB pre-elimination by 2035 and elimination by 2050 in low-incidence countries, it is important to consider additional control measures to prevent the spread of TB, such as LTBI screening. In this context, it is important to quantify the extent of transmission in the country post-immigration, and to set it against possible transmission “en route”, before immigration. We focused on immigrants from high-incidence countries and asylumseekers.

**Design/Methods:** We mapped the extent of transmission of TB between the different risk groups, focusing on TB cases from five countries most represented among TB cases (Morocco, Indonesia, Eritrea, Somalia, India), and native/2nd generation immigrant TB cases (total n=599 cases). We used microsatellite (MIRU-VNTR) and whole genome sequence data in BEAST (BEASTvntr package) to reveal phylogenetic relations between TB cases over 2016-2017. A clustering software, Cluster Picker, helped identify likely transmission events. These events were then mapped in the different nationalities as well as in the 2nd generation immigration versus Dutch. Lastly, an analysis was carried out to identify pre-entry transmission.

**Results:** Transmission occurred mostly within people of same nationality. It was highest in 2nd generation immigrants -forming a bridge between the 1st generation immigrants and Dutch- and in the Eritrean immigrants. Pre-entry transmission was highest in the most recent

wave of immigrants, the Eritrean; when correcting for pre-entry transmission, transmission was similar within the Somali and Eritrean.

**Conclusions:** We discuss the correlates of high transmission post entry, and the implications for control measures.

### OA-32-697-24 High prevalence of smoked illicit substance use in a cohort of patients with drug susceptible TB in Worcester, South Africa

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**Background:** In South Africa, an estimated 4.3% of the population meet diagnostic criteria for an illicit substance use disorder in their lifetime. Illicit substances are primarily smoked in this setting. Smoked illicit substance use may contribute to tuberculosis (TB) transmission, progression from latent TB infection to TB disease, delayed diagnosis, and poor outcomes. However, the prevalence and correlates of smoked illicit substance use among TB patients are poorly documented.

**Design/Methods:** Baseline data on 215 participants initiating drug-susceptible TB treatment in Worcester, South Africa were analyzed to examine smoked illicit substance use prevalence and associations with socio-demographic variables and markers of TB infectiousness. Smoked illicit substance use was defined as self-reported or biologically verified (through urinalysis) methamphetamine, methaqualone, and/or cannabis use. Infectiousness markers included lung cavitation, acid-fast bacilli sputum smear-positivity, and mycobacterial time to culture positivity (TTP).

**Results:** Overall, 114 participants (53%) smoked illicit substances. Of those who self-reported smoked illicit substance use, 27% (n=28) had drug use disorder identification test (DUDIT) scores indicating probable dependence.

Participants who used smoked illicit substances were more likely than those who did not to be male ( $p < 0.001$ ), younger ( $p < 0.001$ ), and underweight ( $p < 0.001$ ). They were also more likely to report tobacco use ( $p = 0.008$ ), use less alcohol ( $p = 0.001$ ), have a smear-positive sputum culture ( $p = 0.003$ ), and have shorter sputum TTP (6.8 vs. 9.1 days,  $p = 0.012$ ) (Table 1).

	No Smoked Substance Use (n=101)	Smoked Substance Use (n=114)	P value
Male (n (%))	48 (47.5%)	82 (71.9%)	< 0.001
Age (years) (median (Q1,Q3))	43 (35, 50)	33 (24, 48)	< 0.001
Underweight BMI <sup>2</sup> (n (%))	48 (47.5%)	78 (68.4%)	< 0.001
HIV positive (n (%))	29 (28.7%)	36 (31.6%)	0.648
Problem alcohol use <sup>3</sup> (n (%))	74 (73.3%)	59 (51.8%)	0.001
Tobacco use <sup>4</sup> (n (%))	61 (60.4%)	88 (77.2%)	0.008
Sputum smear positivity <sup>5</sup> (n (%))	70 (69.3%)	98 (86.0%)	0.003
Sputum culture TTP <sup>6</sup> (n=173) (median (Q1,Q3))	9.1 (5.8, 12.9)	6.8 (5.2, 10.4)	0.012

*Acronyms: TTP- Time to Positivity, AFB- Acid Fast Bacilli, AUDIT - Alcohol Use Disorders Identification Test, PEth - Phosphatidylethanol, BMI- Body Mass Index*

<sup>1</sup>Smoked substance use: self-reported use or positive urine drug test for any of cannabis, methamphetamine, and/or methaqualone.

<sup>2</sup>BMI: Per NHLBI categories, Underweight - BMI less than 18.5

<sup>3</sup>Problem alcohol use: Participants with an AUDIT score of 8 or higher or a dried blood spot PEth value greater than 49 ng/mL.

<sup>4</sup>Tobacco use: Self-reported current smoker

<sup>5</sup>Sputum smear positivity: AFB scanty smear positive or higher for study or clinic sample.

<sup>6</sup>Sputum culture TTP: Contaminated results were excluded.

[Table 1: Baseline Demographics and Clinical Characterization by Smoked Substance Use<sup>1</sup> Status (N=215)]

**Conclusions:** The high prevalence of smoked illicit substance use is unexpected and highlights the need for routine substance use screening of TB patients. Individuals who smoked illicit substances were more likely to be underweight and more infectious than those who did not smoke illicit substances.

These findings suggest delays in treatment seeking and indicate that individuals who smoke illicit substances may disproportionately contribute to community TB spread.

**OA-32-698-24 Evaluating access to and use of TB and HIV services among urban refugees: developing standardized tools**

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**Background and challenges to implementation:** Although national TB and HIV strategic plans often include refugees/asylum seekers (RAS), urban RAS may face challenges accessing host countries' healthcare systems. Little is known about these challenges.

**Intervention or response:** UN Refugee Agency (UNHCR) and U.S. Centers for Disease Control and Prevention developed, tested, and are finalizing knowledge, attitudes, and practices (KAP) tools, evaluating access to primary care, TB, and HIV services for urban RAS and healthcare workers (HCWs). After piloting language-appropriate tools for HCWs and RAS, we used convenience samples of clinic-based and community-based RAS and HCWs to test the tools in South Africa (June 2019) and test revised tools in Cameroon (November 2019). Descriptive analyses were performed.

**Results/Impact:** Although >80% of RAS in both countries (n=418) reported challenges accessing healthcare, only 40% of HCWs (n=50) believed RAS faced challenges. Most RAS relied on public-sector clinics/hospitals, had received HIV testing, and believed they could access TB services (Table).

	South Africa	Cameroon
<b>Healthcare Workers, n</b>	23	27
RAS have challenges accessing care (%)	43%	37%
Provide translation services (%)	0%	41%
<b>RAS*, n</b>	194	224
Challenges accessing care (%)	83%	87%
Use public clinics and hospitals (%)	97%	88%
Could access TB diagnosis (%)	95%	90%
Could access TB treatment (%)	95%	90%
Been tested for HIV (%)	94%	85%

\*RAS, self-reported adults

[Table. Findings on access and use among healthcare workers and refugees and asylum seekers (RAS), June and November 2019]

Perceived barriers to healthcare access differed by country. In South Africa, RAS reported discrimination (51%), denial of care (25%), cost (20%), and long wait times (20%). In Cameroon, RAS reported cost (55%), medi-

cation stockouts requiring patient purchase (20%), discrimination (18%), and lack of transportation (18%). In both countries, HCWs reported lack of translation services and healthcare avoidance by RAS without valid refugee/asylum certificates as the commonest challenges in caring for RAS. KAP tools can be used to identify RAS' challenges to accessing health care.

**Conclusions:** Healthcare access challenges remain for RAS and perceptions of those challenges differ between the two countries assessed and between HCWs and RAS. However, HIV testing and perceived access to TB services were high. UNHCR will collaborate with national TB program colleagues to address challenges and educate HCWs on RAS rights. UNHCR will incorporate these KAP tools into a manual for use in other countries as challenges and solutions may differ.

**OA-32-699-24 Results of the 2019 pilot project on the tuberculosis (TB) screening for residents in Shanty Towns in South Korea**

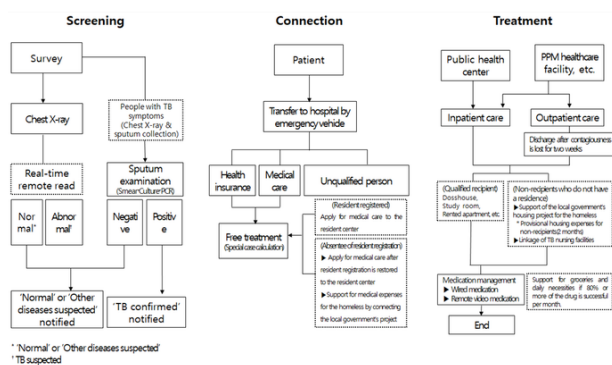
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**Background:** The Korea Centers for Disease Control and Prevention (KCDC) conducted a tuberculosis (TB) screening pilot project for residents in several shanty towns (known as Chok-bang) in 2019. The aim was to develop TB screening and treatment protocols that will help strengthen the TB management for homeless people.

**Design/Methods:** The TB screening personnel visited shanty towns, conducted a survey of the residents, and administered a chest X-ray test for them by using mobile-equipment. Sputum was collected for sputum tests (smear-culture-PCR) from the following residents: the residents who have coughed for more than 2-weeks, and the residents who had a history of TB or were suspected of having active-TB, based on the results of the real-time remote interpretation of the chest X-ray.

**Results:** Out of the 500 subjects for the project, 483 participated in the TB screening. Chest X-rays (482) and sputum testing (141) showed that 3 subjects had tuberculosis. This corresponds to 621 TB patients per 100,000. This is approximately 13 times higher than the TB incidence in the general population (46.4 per 100,000, based on the 2019). The TB screening results are as follows: 20.1% (97/482) in abnormal findings rate of chest X-rays, 0.7% (1/141) in smear-positive rate, 2.1% (3/141) in culture-positive rate, and 2.1% (3/141) in PCR-positive rate. The three patients, diagnosed with TB, had the following features: medical-care recipients, ineligibility for health-insurance, males aged 40-50 years, underlying diseases, smoking, and drinking. Two of the three patients had no history of TB, and they were diagnosed with extensive drug-resistance and isoniazid mono-resistance TB.





[Figure 1. Protocol for the management of tuberculosis (TB) screening and treatment for homeless people]

**Conclusions:** For an early detection and successful treatment of TB patients living on the peripheries of society, a blind spot for TB management, it is essential to enhance access to TB-testing by using mobile chest X-ray equipment. Also, for confirmed TB patients, it is essential to create an environment for treatment support by providing housing and living expenses.

### OA-32-700-24 Are humanitarian organisations capable of implementing complex clinical trials? Key insights from a Phase II/III MDR-TB drug trial designed to produce registration standard data (TB-PRACTECAL-NCT02589782)

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**Background:** Medicine Sans Frontiers (MSF) has implemented a clinical trial to respond to an urgent unmet need. TB-PRACTECAL is a regulatory-level phase II/III randomised controlled trial studying six-month oral regimens containing bedaquiline and pretomanid for MDR-TB. MSF, in partnership with Ministries of Health and third-sector organizations in Uzbekistan, Belarus and South Africa has opened 6 trial sites. We aim to share innovative approaches for consideration by humanitarian organisations when implementing complex clinical trials.

#### Design/Methods:

**Strategic collaboration:** The Sponsor team includes academic partners (LSHTM, UCL), drug-development experts (DNDi), research implementation experts (Swiss TPH) and an MSF nucleus.

**Governance:** A Steering Committee (academic and industry) and an independent Scientific Advisory Committee guides the Project Team. A Data and Safety Monitoring Board provides safety oversight.

**Site selection and partnering:** Sites were selected based on MDR-TB programmatic or research experience, local collaboration and patient recruitment potential. Support models included MSF integration (direct pa-

tient management), MSF supporting the MoH or implementation through a third-party (comprehensive funding/per-patient basis).

**Site development:** Site medical, laboratory and pharmaceutical facilities, existing research HR and medical supply infrastructure was assessed. A development programme enabled trial implementation in line with international guidelines on patient safety, data integrity and ethical research. This included infrastructure upgrades, development of medical, pharmacy and laboratory systems, specialist HR deployments/institutional incentive contracts and specialist trainings.

**Site monitoring:** Risk-based system utilizing on-site visits, remote data monitoring and weekly teleconferences with sites.

**Results:** As of April 2020, 393 patients have been randomized. No critical protocol deviations and data quality and patient safety continue to be deemed satisfactory by the Data Safety and Monitoring Board.

**Conclusions:** With key research capacity building innovations; such as tailored financial and logistic investment, context specific partnering, robust governance and the right organisational competencies, regulatory level clinical research can be setup and led by humanitarian organisations, such as MSF.

### OA-33 Overcoming impediments in tobacco control

#### OA-33-701-24 Monitoring and comparison of the global tobacco and alcohol industry's response to Covid-19 pandemic

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**Background:** According to the World Health Organization (WHO), tobacco and alcohol use has significant negative outcomes to health and wellbeing of humankind during Covid-19 pandemic. Even the total impacts are still unknown, its potential outcomes assumed to be severe. With the growing resistance to tobacco and alcohol industries on sales and marketing, industries change their strategic plans to regain the market and reputation through alternative pathways. This study compares the responses of both industries to the pandemic.

**Design/Methods:** An explorative, qualitative study was conducted using industry websites and publications, journal articles, statements from global health agency and government officials, newspapers and social media platforms on industry response to Covid-19. A conceptual model was developed to compare the two industries and recommendations are made to overcome industry interferences, for the success in containing the pandemic.

**Results:** In the analysis, it was observed that tobacco and alcohol industries use similar strategic responses for their commercial interests during the pandemic. Such as increased focus on Corporate Social responsibility (CSR) through material and money donations, policy interventions in related to Covid-19 related regulations of tobacco and alcohol products sale and manufacturing and attempts to confuse the science around smoking and alcohol use during the pandemic and efforts to use that confusion to promote their platform products.

**Conclusions:** Therefore, the consistent monitoring and comparison of above industries will give insights about industry behaviour on coping the pressures from many health agencies like WHO and presume the industry counteractions via CSR projects, to lobby politicians and governments for forthcoming Covid-19 related policies. Exposing the industry CSR projects and its hidden commercial interests along with advocating politicians will better strive against the lobby pressure of tobacco and alcohol industries during the pandemic.

### OA-33-702-24 The violation of smoke-free workplace policy in Bali, Indonesia and the next strategies to improve compliance

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**Background:** Smoke-free workplace policy is a part of smoke-free law implementation in Bali Province. It is important to raise awareness of smoking harm, encourages smoking cessation and increase productivity. This study aimed to assess the violations of smoke-free workplace policy.

**Design/Methods:** This was a survey at workplaces in Bali Province, Indonesia from January until February 2020. The workplaces were divided into government workplaces that run for public services and private workplaces that owned by company for business. Sample at each strata were selected probability proportional to size. Data collection following time and area observation guidelines, start indoor and continued outdoor. Violations observation at least 20 minutes for each workplace using open data kit mobile application.

**Results:** This study succeeded to observe 325 (65.9%) government and 168 (34.1%) private workplaces that represent ratio in population 2:1. Violation of any evidences regarding indoor smoking were higher in government (33.9%) compare to private (11.9%). The violation detail consist of presence people smoking: 10.8% vs 3.0%, cigarette butts: 24.3% vs 8.9%, e-cigarette using: 1.9% vs 0.6% and smell of cigarette smoke: 18.8% vs 5.4%. Indoor ashtray provision was higher in

government (21.9%) compare to private (9.5%). It has strong association to the violation (OR=14.3, 95% CI: 8.1-25.8). Meanwhile the no-smoking signage was much higher in government (73.5%) compare to private (35.1%).

**Conclusions:** High violation on presence butts, cigarette smoke smell and ashtray provision show the ignorance and low awareness of manager and employee in the area. The implementation of smoke-free workplace policy in government office was inconsistent, they put the sign but they did not comply. No-smoking signage and ashtray elimination should mandatory in government and private workplaces. Stronger strategies should implement in government workplaces such as workshop and supervision for office manager, internal monitoring team building at each area to prevent violation and random inspection for enforcement.

### OA-33-703-24 Recent smoking cessation in tuberculosis patients and risk for tuberculosis infection in child household contacts

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**Background:** Although previous studies have shown that smoking cessation in tuberculosis patients improves treatment outcomes, none have directly measured the impact of smoking cessation on the transmission of tuberculosis. Here, we studied the impact of smoking cessation in tuberculosis patients on the risk for tuberculosis infection in child household contacts.

**Design/Methods:** Between 2009 and 2012, we enrolled and followed 4,500 pulmonary tuberculosis patients in Lima, Peru. We obtained the smoking history and status (classified as had never smoked, actively smoked, recently quit, or quit in the distant past) in 4,406 of these patients. Those who had stopped smoking within two months prior to time of diagnosis were classified as recent quitters. We quantified smoking intensities as either light or heavy. We used a modified Poisson generalized estimating equation to estimate the prevalence ratio (PR) for baseline tuberculosis infection in child contacts.

**Results:** Among 4,877 child contacts, 1,186 (24.3%) were TST-positive at baseline. Compared to child contacts exposed to tuberculosis patients who had never smoked, those exposed to patients who had recently quit heavy smoking were equally likely of being TST-positive at baseline (adjusted PR, 0.97, 95% CI, 0.57-

1.67). The adjusted PR (95% CI) for child contacts of active heavy smokers compared with those who had never smoked was 2.29 (1.45–3.60). We observed similar results when comparing child contacts of patients who had recently quit light smoking with those of active light smokers.

**Conclusions:** Children exposed to tuberculosis patients who had quit smoking within two months prior to diagnosis had a similar infection risk as those exposed to patients who had never smoked. As the onset of tuberculosis symptoms usually occurs several months prior to time of diagnosis, promoting smoking cessation at or before the time of symptom onset may help reduce transmission in settings with high tuberculosis and tobacco consumption rates.

### OA-33-704-24 Effectiveness of behavioural counselling with nicotine gum versus behavioural counselling among tuberculosis patients visiting Directly Observed Treatment Short-Course (Dots) Centres in Delhi, India

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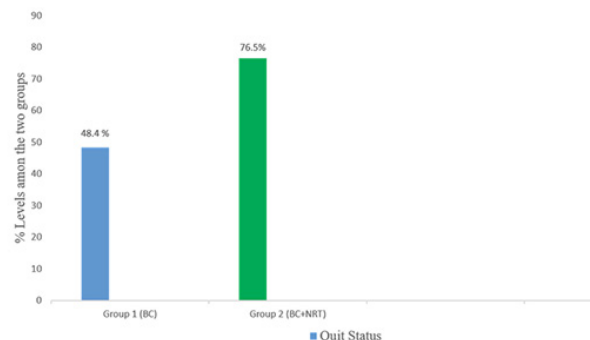
**Background:** Tobacco and Tuberculosis (TB) are world's two greatest public health problems. An estimated 1.3 billion people use tobacco products, with the majority from low or middle-income countries. Exposure to tobacco has been shown to be associated with higher risk of tuberculous infection.

**Design/Methods:** The current study is a „parallel time series“ clinical trial on TB patients attending the DOTS centres in Delhi who used tobacco in any form. Centers were randomly assigned to two intervention groups: integrated intervention using Behavioural counselling with nicotine replacement therapy gum and Behavioural counselling alone (45 each in intervention and control group). Prior to initiation of the interventions, TB patients were assessed through a structured questionnaire. Motivational Ladder and Transtheoretical Model of Stages of Change were used to assess readiness to change the tobacco habit. Study subjects underwent Motivational interviewing.

The subjects were followed at different time interval for tobacco cessation. The quit status was assessed at 1st week, 1st month, 3rd month & 6th month and biochemically verified urine cotinine levels will be performed at baseline & 6th month.

**Results:** Surprisingly, 92.2% in integrated intervention and 95.3% in Behavioural counselling had never made a quit tobacco attempt. There was a linear effect on both 7-day point prevalence abstinence and continuous abstinence was observed over time in the intervention group.

At the end of 1st month, patients who received the integrated intervention had significantly higher rate of success in quitting tobacco when compared with those who received Behavioural counselling (76.5% vs. 48.4%;  $p=0.02$ ).



[Figure 1. Showing quit status at the end of 1st month]

**Conclusions:** DOTS with tobacco cessation should be presented to every tobacco user with TB contemplating to quit the habit. Few studies are done in other parts of the world using brief advice only on smokers. Tobacco cessation may be beneficial and confer advantages on future health outcomes of TB patients who quit tobacco use.

### OA-33-706-24 The investment case for tobacco control in five sub-Saharan African countries - a return on investment analysis

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**Background:** Tobacco use is a leading threat to public health worldwide, and a major risk factor for non-communicable diseases. Proven solutions exist, yet few countries have comprehensively implemented the WHO Framework on Tobacco Control (FCTC) demand-reduction measures. We estimate tobacco-attributable health and economic costs in five countries in sub-Saharan Africa, and the potential return on investment (ROI) of six FCTC measures.

**Design/Methods:** An RTI-developed model is populated with data on mortality and morbidity (total and tobacco-attributable) from the IHME Global Burden of Disease database. We calculate tobacco-attributable medical costs using a smoking-attributable fraction approach; productivity losses due to premature mortality using a human capital approach, and; losses due to workplace absenteeism and presenteeism based on parameters from the literature. Next, we assess each country's current level of FCTC implementation, and the extent to which full implementation of six measures could

alter health and economic outcomes over a 15-year period. We use the WHO NCD Costing Tool to evaluate the measures' financial costs, and compare costs and economic benefits to calculate the ROI of the measures, individually and as a policy package.

**Results:** Although smoking prevalence in sub-Saharan Africa is currently lower than in many other regions of the world, tobacco still costs between 0.5 and 1.5% of GDP in the countries of our analysis. Implementing proven FCTC measures could save nearly 102,000 lives over the next 15 years. All policies have ROIs greater than one, with increased taxes and bans on tobacco advertising, promotion, and sponsorship generally demonstrating the highest ROI.

**Conclusions:** Tobacco use is increasing rapidly in Africa and the burden is predicted to rise. Our national-level analysis demonstrates the return to countries fulfilling their FCTC obligations. By investing now in tobacco control policies, countries can not only improve health, but also reduce health expenditures and grow the economy.

## OA-34 Risk factors, surveillance and control strategies in potential zoonotic TB hotspots

### OA-34-707-24 Clustering of Moroccan and Spanish *Mycobacterium bovis* isolates from slaughtered cattle

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**Background:** Livestock production is an important pillar of the Moroccan economy; however, the problems facing the industry are complex and include infectious diseases. Bovine tuberculosis, caused primarily by *Mycobacterium bovis*, is not considered a high priority in Morocco. Nevertheless, it has been shown to generate considerable direct and indirect economic losses, in addition to the unknown human health burden caused by zoonotic transmission. In Morocco, the molecular genetic patterns from *Mycobacterium bovis* isolates

have been previously assessed using deletion PCR and spoligotyping. The results suggest *M. bovis* transmission channels between Morocco and Southern Europe. In this study, we investigated a larger set of *M. bovis* genetic profiles to define the phylogenetic links between Moroccan isolates and those found worldwide.

**Design/Methods:** A total of 57 isolates were included in this study, 53 met the quality criteria for Illumina sequencing performed using a Mi-Seq at the USDA-NVSL laboratories in Ames-Iowa. The analysis of the sequencing results was performed using an NVSL in-house bioinformatics pipeline, publicly available at <https://github.com/USDA-VS/vSNP>

**Results:** Morocco tries to be self-sufficient in its consumption of bovine meat and milk products but importing cattle from regional suppliers does regularly occur. However, much of this importation and intra-country movement is not well regulated. The results of the present study show close clustering between Moroccan and Spanish isolates, which is supported by the economic and cultural history. Some less strong clustering was found with isolates from Eritrea, USA and Mexico and the only French isolate available at the time of the analysis in the NVSL database.

**Conclusions:** Based on the phylogenetic results, whole genome sequencing provides great insight into *M. bovis* transmission dynamics. Ultimately, a quality database of whole genome sequences from well characterized wildlife and livestock can offer critical information on *M. bovis* transmission dynamics within the animal-human interface in Morocco and the surrounding regions.

### OA-34-708-24 Spoligotyping based direct detection and Identification of *Mycobacterium tuberculosis* complex from cattle samples

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**Background:** Bovine tuberculosis (bTB) is a chronic illness in animals, especially in cattle, leading to loss in the productivity and signifies a crucial public health risk. Speciation of *Mycobacterium tuberculosis* complex (MTBC) in cattle is important to understand the dynamics of disease transmission between human and cattle. In this study, we describe the spoligotyping based speciation of MTBC from nasal swab and milk samples from cattle.

**Design/Methods:** We identified 4 livestock farms in Chennai, India to screen cattle for tuberculosis. A total of 381 cattle were screened by comparative intradermal

tuberculin (CIT) skin testing. From CIT positive animals nasal swab and milk samples were collected. DNA was extracted from the samples for spoligotyping. The spoligotyping data were compared in SITVIT 2 database.

**Results:** Out of 381 cattle, 40 animals were found positive for CIT. Nasal swabs were collected from all the CIT positive animals and from 23 animals milk samples also obtained. From the biological samples obtained from CIT positive animals, 27 were positive by spoligotyping including two milk samples.

Spoligotyping data indicated the presence of *M.tuberculosis*, *M.bovis* and *M.orygis* strains in cattle. Out of 27 positive spoligotyping samples, 22 samples were *M.tuberculosis*, one sample was *M.bovis* and two samples were *M.orygis*.

Most of *M. tuberculosis* strains were belonged to Manu1 Lineage followed by East African Indian (EAI) lineage. One Beijing lineage was also detected from the samples. Most of the spoligotypes were matched with SITVIT database except 2 samples.

**Conclusions:** Our study confirms predominantly presence of *M.tuberculosis* spoligotypes in cattle. This results suggesting that the infection rate of *M. tuberculosis* among animals might be higher in India than previously thought. There is a need for multi-centric study across India to understand the national prevalence, acquisition, and transmission of *M. tuberculosis* within animals and from animal to animal handlers vice versa.

#### OA-34-709-24 Prevalence and risk factors of mycobacterial infections among pastoralists and their cattle in southwestern Nigeria

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**Background:** Active case finding and accurate diagnosis of mycobacterial infections are very necessary for developing countries like Nigeria. Of importance, are pastoralists, a neglected group that are unaware of both their health status and that of their livestock. This study evaluated the prevalence of mycobacterial infections and their associated risk factors among pastoralists and their cattle herds.

**Design/Methods:** Through a cross-sectional study design, a sampling of randomly selected pastoral communities in Ibarapa Area, Oyo State was carried out. A "One Health" approach was applied to screen both pastoralists and their cattle. Sputum samples from presumed sub-clinical pulmonary TB patients based on oral

interview were collected, cultured and genotyped. Cattle herds were concurrently screened using the single intradermal comparative cervical tuberculin test with an OIE standard of  $\geq 4$ mm. Descriptive statistics and odds ratios (OR) were calculated. Chi-square test was used to determine the level of significance at a 95% confidence interval. Predictors of mycobacterial infections were determined using logistic regression.

**Results:** Overall, 150 pastoralists were screened and (17/150; 11.3%) were positive to mycobacteria culture, out of which three *M. tuberculosis* (3/150; 2%) and 14 *M. avium* (14/150; 9.3%) were identified. No significant statistical association was observed. Further, 842 cattle were screened from 98 herds, 18 cattle were positive reactors to bovine tuberculosis (BTB) giving an individual animal prevalence of 2.1% and herd prevalence of 16.3%. Cattle herd size  $>50$  (OR = 9.1; 95% CI 1.1–76.8) was identified as an associated risk factor for BTB.

**Conclusions:** We confirm the presence of undetected pulmonary TB and non-tuberculous mycobacterial infection among the pastoralists and BTB in their cattle herds. We recommend further studies on the possible ongoing zoonotic transmission of *M. bovis* in pastoral communities.

#### OA-34-710-24 Facility-based characteristics are strong predictors of poor tuberculosis treatment outcomes in children in Pakistan

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**Background:** Few studies have examined predictors of poor TB treatment outcomes among children without HIV infection. We aim to identify predictors of unsuccessful pediatric treatment outcomes in Pakistan.

**Design/Methods:** We implemented an intensified case-finding program in Pakistan, where children ( $<15$  years) seeking health care at four participating facilities were verbally screened for TB symptoms and exposure and, if present, evaluated for TB disease. Children started TB treatment as per national guidelines. We assessed unsuccessful outcomes (death, treatment failure, lost-to-follow-up). We examined children's demographic and clinical characteristics, and the facility type using multivariable logistic regression.

**Results:** A total of 1,404 children initiated treatment for drug-susceptible TB; 17.5% were extra-pulmonary. The median age was 4 years (IQR: 2-8), 43.7% were female, and 84.1% were malnourished. Children presented with the following symptoms: 91.5% cough, 84.5% fever, and

75.6% weight loss. Lymph node examinations were suggestive of TB in 10.8% of children. Only 5.6% of children were diagnosed in a newly established TB facility and 18.4% in a rural facility. Unsuccessful treatment outcomes were experienced by only 4.8% of children (2.4% lost to follow-up, 1.4% treatment failure, 1.0% died). Lymph node exam results (OR: 1.50; p:0.041) and a newly established facility (OR: 1.81; p:0.001) were positively associated and rural facilities (OR: 0.19; p:0.04) were negatively associated with unsuccessful treatment outcome.

Variable	Univariate Analysis OR (95% CI)	p-value	Multivariable Analysis OR (95% CI)	p-value
Female	1.09 (0.67, 1.78)	0.734	0.99 (0.77, 1.28)	0.983
Age	1.01 (0.95, 1.07)	0.719	1.00 (0.94, 1.07)	0.975
Malnutrition	2.38 (0.95, 6.01)	0.066	0.83 (0.47, 1.45)	0.513
Fever	1.96 (0.84, 4.60)	0.120	1.51 (0.98, 2.33)	0.062
Lymph node exam suggestive of TB	1.93 (1.00, 3.70)	0.049	1.50 (1.02, 2.21)	0.041
Newly established facility	5.36 (2.82, 10.18)	<0.001	1.81 (1.27, 2.58)	0.001
Rural Facility	0.06 (0.01, 0.45)	0.006	0.19 (0.06, 0.59)	0.004

[Table.]

**Conclusions:** Among children treated for TB disease, lymph node examinations may be a useful indicator of the likelihood of an unsuccessful outcome. Newly established facilities require time and investment in processes to reduce LTFU, the majority of poor outcomes experienced. Rural facilities see fewer patients, allowing for more resources to be allocated per child, leading to better treatment outcomes. Urban facilities were referral centers that see sicker patients and those traveling longer distances, leading to poorer outcomes.

**OA-34-711-24 Diagnostic utility of microbiological and histopathological testing in the diagnosis of paediatric TB lymphadenitis in Indian children screened for the SHINE trial**

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**Background:** Diagnosis of tuberculosis lymphadenitis (LNTB) in children poses a challenge due to wide range of differential diagnoses. We evaluated the utility of microbiological and histopathological testing of fine needle aspiration (FNA) and/or lymph node (LN) biopsy to confirm LNTB

**Design/Methods:** We undertook a retrospective study of microbiological (AFB smear, Xpert MTB/RIF, LJ and MGIT cultures) and histopathology testing of peripheral LN samples from children aged <16 years, suspected to have LNTB and screened for the SHINE trial in Indian sites (Chennai and Pune). SHINE is a TB treatment shortening trial in children with non-severe TB (ISRCTN63579542)

**Results:** Of 194 patients with enlarged LNs screened between July 2017 and September 2018 (52% males, median [IQR] age 7[4, 10], 177(91%) had enlarged cervical lymph nodes); 172(89%) were sampled by FNA and 22(11%) by biopsy.

Of 105 children treated for TB, TB was microbiologically confirmed in 84(80%): 31(30%) had positive Xpert MTB/RIF (of these 5 AFB smear-positive), 53(50%) positive TB culture; 69(66%) had histopathology results suggestive of TB (Table).

Of the screened patients, 13 had repeat LN samples due to inconclusive results: 10(77%) had LN biopsy and 3(23%) FNA. LNTB was diagnosed in 10(100%) patients with repeat LN biopsy: 3 had microbiologically-confirmed TB (all Xpert MTB/RIF and TB culture-positive, 1 AFB smear-positive), and all had histopathology suggestive of TB. No TB was confirmed on repeat FNA. Of 89 children not treated for TB, 49(55%) had reactive lymphadenitis, 28(31%) suppurative lymphadenitis, 2(2%) BCG adenitis, 1 lymphoproliferative disorder, 1 branchial cyst and 8(9%) had inconclusive results.

Histopathology reports #	Treated for TB	Microbiologically confirmed TB	AFB smear positive*	Xpert Mtb/RIF positive^A	Positive only by TB culture~
TB features #(n=79)	69 (87%)	65 (82%)	2 (3%)	20 (25%)	45 (57%)
Suppuration (n=39)	25 (64%)	12 (31%)	1 (3%)	9 (23%)	3 (8%)
Other non-TB features (n=68)	11 (16%)	7 (10%)	2 (3%)	2 (3%)	5 (7%)
Inconclusive final results (n=8)	0	0	0	0	0
Total (n=194)	105 (54%)	84 (43%)	5 (3%)	31 (16%)	53 (27%)

[Table. Lymphnode results of paediatric lymphadenitis]

**Conclusions:** A combination of microbiological and histopathological tests confirmed LNTB in 80% children treated for TB and helped to establish diagnosis in the majority of children with non-TB lymphadenitis. Lymph node biopsy could be considered over FNA for repeat LN evaluation to aid the diagnosis of LNTB.



### OA-34-712-24 Thirty-year follow up of a double-blind randomised placebo-controlled trial of repeat Bacillus Calmette-Guérin vaccination in northern Malawi

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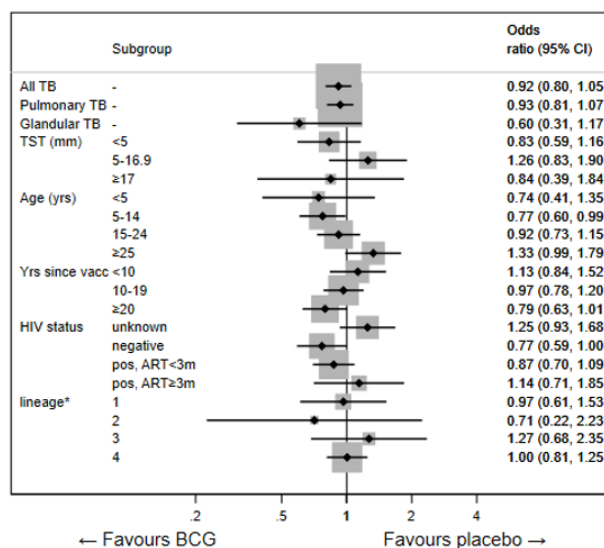
**Background:** The double-blind randomised controlled Karonga Prevention Trial of repeat Bacillus Calmette-Guérin (BCG) vaccination found 49% efficacy against leprosy but no protection against tuberculosis after 6 years of follow-up in 1995. Additional follow-up greatly increases tuberculosis case numbers, allowing subgroup analysis.

**Design/Methods:** Nearly 47000 individuals (all ages) were randomised in Karonga District, northern Malawi, 1986–89, to receive a second BCG vaccination or placebo if they had a BCG vaccine scar. Enhanced passive surveillance ensured microbiological assessment of individuals with tuberculosis symptoms up to 2018. Total population follow-up was available in part of the district: there were no differences in mortality by vaccine group so analysis used odds ratios (ORs).

Tuberculosis events were included if they were microbiologically or histologically confirmed (excluding those with single scanty smear). Prespecified subgroup analyses were: tuberculosis type, vaccination age, time since vaccination, prior tuberculin status, HIV status and M tuberculosis lineage.

**Results:** There were 824 tuberculosis events: 786 pulmonary, 37 glandular. There was no effect of second BCG overall (OR 0.92 [BCG vs placebo] 95% confidence interval 0.80-1.05), for pulmonary tuberculosis (0.93, 0.81-1.07), or for glandular tuberculosis (0.60, 0.31-1.17). The ORs for individuals <15 years at vaccination were slightly lower ( $p=0.04$  for interaction with age). The OR was also lower for those with known HIV-negative tuberculosis (OR 0.77, 0.59-1.00) There were no differences by tuberculin status, lineage, or time since vaccination.

**Conclusions:** These data provide no support for repeat BCG vaccination for pulmonary tuberculosis control in this rural African population. Weak evidence of effect in subgroups should not be over-interpreted given the multiple analyses conducted. Observational studies in this population have found no evidence that an initial dose of BCG provided protection against tuberculosis, and immunological studies have provided evidence that widespread exposure to environmental mycobacteria may have masked any protection imparted by BCG.



[Figure. Overall effects (BCG vs placebo) and by subgroup (for pulmonary TB), among BCG scar + ves]

### OA-35 New and existing TB drug resistance

#### OA-35-713-24 Delayed killing of MTB in Molecular Bacterial Load Assay early during treatment in relapse patients

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**Background:** Reliable markers for monitoring TB treatment response could accelerate clinical trials and enable personalized treatment. We evaluated the Molecular Bacterial Load Assay (MBLA) that enumerates MTB measuring rRNA as a marker to determine TB treatment responses.



**Design/Methods:** Patients from the PanACEA MAMS TB-01 trial were followed up until 6 months after end of treatment, and an outcome of relapse, cure, or no information was assigned, based on eventual need for re-treatment. Bacterial load from repeated sputum samples was measured by MGIT Time To Detection (TTP) and by MBLA. We analysed the natural log scaled MBLA and TTP using non-parametric methods at observed time points to compare between outcome groups. Linear Mixed Models were used for estimating inter- and intra-individual variation over time with quadratic time effects to describe bacterial load changes.

**Results:** 4 patients required re-treatment due to symptoms and positive bacteriology during follow-up. 132 achieved cure, and in 11 cases, not enough certainty was achieved to ascertain an outcome.

MBLA outcomes (scaled at  $\log(\text{mean MBLA}+1)$ ) were earlier in detecting group-wise differences between the relapse and the healthy groups at week two (Mean (SD) Cured-1.420 (0.428) vs. Relapsed 1.786 (0.079),  $p=0.02$ ) and three (Mean (SD) Cured- 1.241 (0.508) vs. Relapsed 1.740 (0.035),  $p=0.02$ ), with more consistency from week six (figure). For MGIT TTP, the group-wise difference was not significantly different until week 9. Estimates of the longitudinal data showed a statistically significant difference for the relapse group in both linear and quadratic time effects for MBLA but not for TTP.

**Conclusions:** MBLA shows a significant difference between patients with good, and poor long-term outcome early in treatment. This supports the use of MBLA as an endpoint in future clinical trials. Use of this test for individualized therapy may be possible, but requires larger studies with prospective evaluation of decision algorithms.

## OA-35-714-24 Bedaquiline resistance in *Mycobacterium tuberculosis* predates its clinical use

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**Background:** Bedaquiline has become a key drug for treatment of drug-resistant tuberculosis. Most clinical resistance is conferred by mutations in *Rv0678*, which encodes a negative repressor of the MmpL5 efflux pump and confers clofazimine cross-resistance. Here, we estimate the date of emergence of several *Rv0678* variants in global *Mycobacterium tuberculosis* lineages.

**Design/Methods:** We constructed global whole genome sequence datasets of thousands of lineage 2 and 4 isolates using newly generated and publicly available data. We enriched these by screening public repositories for sequences containing all previously reported *Rv0678* variants. We built a whole genome maximum likelihood phylogenetic tree using RAxML-NG and dated the nodes of this phylogeny using BactDating. The lineage 2 dataset contained 1514 sequences from isolates collected between 1994-2019. The lineage 4 dataset contained 2168 sequences including three 18th century mummies.

**Results:** We identified 483 non-synonymous and promoter variants in 439 sequences. 25 sequences were from isolates collected prior to bedaquiline clinical trials in 2007 and 21 of these contained bedaquiline resistance-associated variants. Most *Rv0678* mutations occurred in sequences carrying other resistance variants. In lineage 2 we identify 28 unique emergences of resistance estimated to have occurred between 1995-2018 (Figure). In lineage 4 we identify 44 unique emergences estimated

to have occurred between 1851-2019 (Figure). We also identified a clade of 65 samples carrying the Ile67fs variant that we estimated to have arisen in 1872 (1823-1908). This predates the first use of clofazimine or bedaquiline. Bayesian skyline analysis of this clade shows that it has expanded since 1950, coinciding with the development of clofazimine.

**Conclusions:** *Rv0678* mutations conferring bedaquiline/clofazimine resistance have been in circulation since before the antibiotic era, implying non-synonymous mutations in *Rv0678* have little fitness cost. This pre-existing reservoir of resistant strains is likely to expand with increasing bedaquiline and clofazimine use.

### OA-35-715-24 Primary bedaquiline resistance among drug-resistant tuberculosis cases in Taiwan

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**Background:** Bedaquiline (BDQ), a novel and effective antimycobacterial drug, recommended by WHO for use in combination for treating drug-resistant tuberculosis (TB) was introduced to Taiwan in 2014. Since the emergence of BDQ resistance is alarming, we have conducted BDQ resistance analyses for strengthening our drug-resistant TB management program.

**Design/Methods:** This is a retrospective cohort study including initial *Mycobacterium tuberculosis* isolates from 364 drug-resistant TB cases never exposed to BDQ during 2013-2018. We randomly selected 22 (6%) isolates with BDQ MIC <0.25 µg/ml as the control group and collected 39 (10.7%) isolates with BDQ MIC ≥0.25 µg/ml for analyses. Phenotypic drug susceptibility testing (DST) was conducted using the MGIT960 system and the agar proportion method (APM) with critical concentration of 1 µg/ml and 0.25 µg/ml of BDQ, respectively. Sanger sequencing of the *atpE*, *Rv0678* and *pepQ* genes were performed to detect mutations conferring BDQ resistance.

**Results:** All 22 isolates with low BDQ MICs showed wild-type results. Of the 39 cases with high BDQ MICs, 76.9% (30/39) were new TB cases, 79.5% (31/39) were multi-drug-resistant, 12.8% (5/39) were pre-extensively drug-resistant and 7.7% (3/39) were rifampicin-resistant TB. We found 35.9% (14/39) isolates were phenotypically resistant to BDQ either by MGIT960 (N=14) or APM (N=8). Excluding 2 MGIT-BDQ-resistant isolates with borderline resistance (GU400growth control-GU100B-DQ ≤ 1 day), 100% (12/12) isolates harbored *Rv0678* gene mutations, including 6 novel mutations, Ins g 181-182 frameshift mutation, Del 11-63 frameshift mutation, Ile80Ser (2 isolates), Phe100Tyr, Ala102Val, g-14a, and

3 previously reported mutations, Ser53Pro, Leu83Pro, Leu114Pro. Two silent mutations, Glu61Glu (GAG/GAA) and Ala210Ala (GCG/GCA), were revealed in 2 phenotypically (MGIT and APM) BDQ-susceptible isolates with MIC =0.25 µg/ml in the *atpE* and *pepQ* gene, respectively.

**Conclusions:** The overall phenotypic BDQ resistance among drug-resistant TB cases without BDQ exposure was 3.8% (14/364). We recommend applying genotypic BDQ DST for early detection of BDQ susceptibility.

### OA-35-716-24 Mutation in *Mycobacterium tuberculosis* confer resistance to delamanid in drug-naïve patients

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**Background:** Loss of function mutations in F420 genes (*ddn*, or its coenzymes *fgd1*, *fbiA*, *fbiB*, and *fbiC*) can cause resistance to delamanid. We identified delamanid resistance-conferring mutations in *Mtb* strains from TB patients, naïve to delamanid, using whole-genome sequencing (WGS) and minimum inhibitory concentrations (MIC).

**Design/Methods:** *Mtb* isolates and clinical data from HIV-positive and HIV-negative TB patients from Peru, Thailand, Ivory Coast, Democratic Republic of the Congo, Kenya, and South Africa between 2013-2016, were collected. Drug susceptibility testing (DST) at the Swiss National Laboratory for Mycobacteria using micro-dilution and MGIT liquid culture was performed. *Mtb* genomes using Illumina HiSeq 2500 were obtained and screened for mutations using TBprofiler. An MIC of ≥0.04 mg/L using MGIT was classified as resistant.

**Results:** Among 129 *Mtb* isolates, 70 (54%) carried polymorphisms in at least one F420 gene. All 70 patients had no prior history of TB and were naïve to delamanid. MICs of 10 of these isolates were determined. Median age of the 10 patients was 41 years (interquartile range [IQR]: 31-50), two were female, and four HIV-positive.

All 10 received first-line regimens. One isolate, susceptible to isoniazid, rifampicin, ethambutol, pyrazinamide, moxifloxacin, and amikacin, had a synonymous nucleotide change in the gene *fgd1* (T960C) and a deletion in the *ddn* gene (Tyr29del), which were associated with an elevated delamanid MIC (No. 9, Table). This patient died during TB treatment.

No.	Lineage	Mutations in the F <sub>420</sub> genes	MIC mg/L in the micro-dilution	MIC mg/L in the MGIT system
0	H37Rv ATCC 27294	Control (wt)	<0.015	-
1	L4.1.2.1	fgd1 Lys270Met	0.5	>0.32
2	L4.6.2.2	ddn C168T	<0.015	-
3	L2.2.1	fgd1 T960C	<0.015	-
4	L2.2.1	fgd1 T960C	<0.015	-
5	L4.3.2	fbtC C1161T	<0.015	-
6	L4.1.2.1	fgd1 Lys270Met	0.03	<0.32
7	L4.1.2.1	fbtC G-11A fgd1 Lys270Met	<0.015	-
8	L4.1.2	fbtA Ile208Val	<0.015	-
9	L2.2.1	fgd1 T960C ddn 85-87del (Tyr29del)	>8	>0.32
10	L1.1.1	fbtC Ala416Val, Trp678Gly fgd1 Arg64Ser, T960C	0.03	<0.32

Abbreviations: MIC, minimal inhibitory concentration; No, number; MGIT, Mycobacteria Growth Indicator Tube; L, lineage; wt, wild-type.

[Table 1. Polymorphisms in F<sub>420</sub> genes and minimal inhibitory concentration values for delamanid]

**Conclusions:** The nonsynonymous ddn mutation Tyr29del, a natural polymorphism, may confer an increased delamanid MIC. Mtb isolates with naturally elevated MICs to delamanid from previously untreated patients suggests delamanid DST determination may be indicated prior to treatment.

### OA-35-717-24 Heteroresistance as a predictor of treatment outcome among patients with drug-resistant tuberculosis in the Philippines

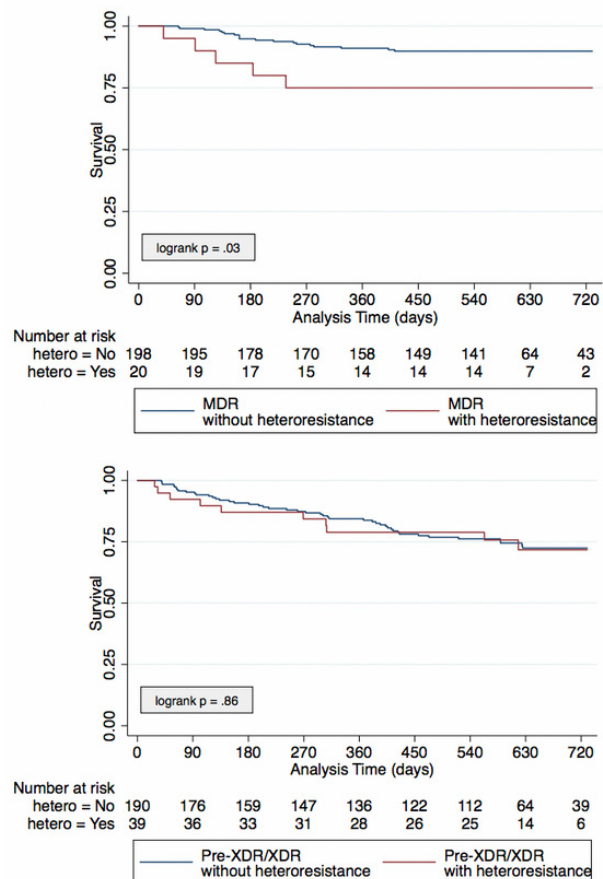
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**Background:** Targeted deep sequencing has revealed mixed populations of susceptible and resistant bacilli (i.e., heteroresistance) in patients with drug-resistant tuberculosis (TB). However, the impact of heteroresistance on treatment outcomes is not known.

**Design/Methods:** We performed targeted deep sequencing with single molecule-overlapping reads (SMOR) to identify heteroresistance in banked culture isolates from patients treated for drug-resistant TB between 2013-2016 in the Philippines. The association between heteroresistance and time to unfavorable treatment outcome (death or treatment failure) was assessed using non-parametric log-rank tests and cox proportional hazards regression, controlling for known demographic and clin-

ical risk factors (age, sex, body mass index, region of the Philippines, cavitory chest X-ray, baseline sputum smear grade, and drug resistance type).

**Results:** 448 isolates (218 MDR, 220 pre-XDR, and 10 XDR) from patients who survived past the first month of treatment were included. 59 (13%) had heteroresistance to isoniazid, rifampin, fluoroquinolones and/or second-line injectables. Heteroresistance to fluoroquinolones was more common than heteroresistance to other drug classes (9% vs. ≤2%), and thus more common among pre-XDR/XDR TB than MDR TB isolates (66% vs. 34%, p=0.02). Log-rank tests showed significant association between heteroresistance and time to unfavorable treatment outcome for patients with MDR TB, but not pre-XDR/XDR TB (Figure 1). In multivariable analysis, heteroresistance was strongly associated with time to unfavorable treatment outcome among patients with MDR TB (adjusted hazard ratio [aHR] 4.62 (95% CI 1.57 to 13.58), but not pre-XDR/XDR TB (aHR 0.94, 95% CI 0.45 to 1.96).



[Figure 1. Association between heteroresistance and time to unfavorable treatment outcome. Time to unfavorable outcome (death or treatment failure) was shorter when heteroresistance was present for patients with MDR TB (top panel, N=218, p=0.03), but not for patients with pre-XDR/XDR TB (bottom panel, N=230, P=0.86)]

**Conclusions:** We identified heteroresistance as a novel baseline risk factor for unfavorable treatment outcome among patients with MDR TB. This finding suggests that poor outcomes are in part due to inadequate treatment of drug resistant sub-populations below the threshold of detection for phenotypic drug susceptibility testing and/or treatment of drug susceptible populations with second-line drugs.

### OA-35-718-24 Genomic context of drug resistance among *Mycobacterium tuberculosis* in Romania

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**Background:** Tuberculosis continues to represent a major health problem worldwide. Countries in Eastern Europe have the highest incidence of multidrug-resistant (MDR-TB) worldwide, with some countries reporting up to 20% of new cases and 60% of retreatment cases already resistant. As part of a larger investigation of DR-TB in the region, we sequenced *M. tuberculosis* clinical isolate genomes from patients in Romania and performed taxonomic, comparative and predictive bioinformatics analysis.

**Design/Methods:** Sputum samples were collected from patients with drug-resistant and drug-sensitive tuberculosis, treated at the National Institute of Pneumology 'Marius Nasta', in Bucharest, Romania. Drug susceptibility testing (DST) and genome sequencing of the clinical isolates were performed. Digital spoligotypes and drug resistance predictions were computed. Genomes from Romania samples were compared to genomes from samples previously collected in Moldova, a neighboring, non-EU state.

**Results:** Genomic analysis revealed that the majority of the isolates were Euro/American lineage (92%), and only 8% were Beijing lineage. This is in contrast to the Moldova samples, where majority of spoligotypes were either H3 (41%) or Beijing (38%). Drug resistance profiles of isolates between Romania and Moldova revealed Streptomycin resistance was more prevalent in the Moldova samples. Within the Drug-resistant group, the majority of Moldova samples were resistant to Isoniazid, whereas the majority of the Romania samples were resistant to Rifampicin.

**Conclusions:** We found that the spoligotype distribution of the Romania samples was more similar to reported stats from western European states, whereas the spoligotypes of the non-EU country Moldova was more similar to non-EU countries, such as Azerbaijan, Russia, and Belarus. We found that DR-TB samples from the two neighboring countries differed in their individual drug resistance. These results could support more directed control measures and treatment options depending on region.

### OA-35-719-24 Minimum inhibitory concentrations variability of *Mycobacterium tuberculosis* Peruvian strains using the UKMYC6 CRyPTIC plate

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**Background:** The Sensititre method use an UKMYC6 plate designed by the CRyPTIC consortium for minimum inhibitory concentrations (MIC) determination of several antituberculosis drugs. This study evaluated the variability of antituberculosis drugs MICs in Peruvian strains.

**Design/Methods:** 574 *Mycobacterium tuberculosis* (MTB) drug-resistant strains stored at the National Institute of health from Peru were selected using a national stratified sampling. All strains were tested using 7H10 Agar Proportion Method (APM) and Sensititre UKMYC6 plate for rifampicin, isoniazid, ethambutol, ethionamide, kanamycin and levofloxacin drugs. Additionally, the UKMYC6 plate allowed the characterization of seven drugs including new (bedaquiline, delamanid) and repurposed (linezolid, clofazimine) ones. MICs were measured after 14 and 21 days of incubation using the Vizion<sup>TM</sup> system. To evaluate concordance, strains were categorized as resistant or susceptible using Critical Concentrations values of APM.

**Results:** 522 (90.9%) strains obtained a readable result in 14 days, whereas 52 (9.1%) in 21 days. The overall categorical agreement for compared drugs was 88% (range: 75% – 95%). Discrepant results percentages for each drug were: rifampicin (11.9%), isoniazid (12.2%), ethambutol (24.9%), ethionamide (15.4%), kanamycin (4.8%) and levofloxacin (4.8%). The average sensitivity for 'rifampicin and isoniazid' was 86.5%, for 'kanamycin and levofloxacin' was 66.5%, and for 'ethambutol and ethionamide' was 53%. However, the overall specificity for all six drugs was 98.7%. For most of the drugs, resistant and susceptible strains had clearly different MIC distributions. New and repurposed drugs showed a MIC distribution below critical concentrations corresponding to APM (7H10) and MGIT methods (Figure 1).

**Conclusions:** The UKMYC6 plate allows to obtain a detailed MIC distribution of antituberculosis drugs. MICs had a variable distribution in MTB strains previously categorized as susceptible or resistant according to the reference method (APM). Peruvian MTB strains present a high categorical concordance (88%) between Sensititre and APM methods.

### OA-35-720-24 Pyrazinamide resistance among rifampicin-resistant tuberculosis patients in Yangon, Myanmar: prevalence, clinical characteristics and treatment outcomes

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**Background:** Yangon Region is reported as the highest multidrug-resistant tuberculosis (MDR-TB) burden area in Myanmar. Pyrazinamide (PZA) is one of major drugs of standard regimen and new shorter regimen for MDR-TB and extensively drug resistant TB (XDR-TB). There are limited data of PZA susceptibility as there is no routine drug susceptibility testing (DST) for PZA. The significant impact of PZA resistance on treatment outcome is also a controversy issue.

**Design/Methods:** Xpert RIF/MTB confirmed rifampicin-resistant TB (RR-TB) patients (n=192) enrolled for both conventional and shorter MDR-TB treatment regimen at TB Centers in Yangon, during 2019 were included in the study. Sociodemographic, clinical data and treatment outcome data were collected. RR-TB cases were further investigated to determine XDR-TB using MTBDRsl assay. PZA DST was performed using Mycobacterial Growth Indicator Tube (MGIT) 960. Sanger DNA sequencing was also used to detect mutations in *pncA* genes and its promoter region.

**Results:** Of 192 RR-TB patients, 26 were pre-XDR-TB and 5 were XDR-TB. Phenotypic PZA resistance was detected in 113 (58.9%). Sixty-five different mutations were distributed in *pncA* or its promoter region of PZA resistant isolates. Sociodemographic and clinical characteristics like age, gender, previous TB history and sputum acid fast bacilli status were not associated with PZA susceptibility but PZA resistance was higher in XDR-TB cases ( $p<0.05$ ). Treatment outcome can be evaluated in 82 RR-TB patients who completed shorter MDR-TB treatment regimen and it showed no statistically significant difference between PZA resistant and PZA sensitive groups.

**Conclusions:** High prevalence of PZA resistance in Myanmar RR-TB highlighted the need of effective treatment regimen development for PZA-resistant MDR-TB. Routine PZA susceptibility test should be incorporated to treatment monitoring regimen. Information on PZA resistance associated gene mutations may be beneficial for development of rapid susceptibility assays. Long-term longitudinal studies are needed to evaluate the treatment responses, outcomes and relapse among PZA resistant cases.

### OA-36 The role of pharmacies in the TB cascade of care

#### OA-36-721-24 Improving TB case finding through pharmacies using digital tools in Manila City, Philippines

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**Background and challenges to implementation:** The Philippines has one of the highest TB burdens globally with an estimated incidence of 554/100,000. For many Filipinos, pharmacists are the first point of access to modern medical advice and treatment. The 2016 National TB Prevalence Survey showed that 40% of symptomatic patients did not go to health centers, but instead bought medicines at pharmacies and self-medicated.

**Intervention or response:** In June 2019, USAID's TB Innovations and Health Systems Strengthening in collaboration with mClinica Pharmacy Solutions developed an e-referral tool within the SwipeRx mobile app, a digital network of over 34,000 pharmacy professionals in the Philippines, 90% from the private sector. The tool conveniently provides electronic referral of presumptive TB patients seeking cough or anti-TB medicines without prescriptions, to partner health facilities with TB services. Referred presumptive TB patients automatically receive an SMS message directing them to the nearest TB health center. The outcome of the referral is confirmed through the SMS thread and automatically recorded in SwipeRx.

**Results/Impact:** Pilot implementation was conducted from September 2019 to February 2020. A total of 82 clients with cough symptoms or buying anti-TB medicines without prescriptions were referred to TB facilities. Half of these presumptive TB clients agreed to consultation at the health facilities. Of those, forty percent successfully visited the health facilities. Fifty-four percent of those

who consulted at the facility were diagnosed with TB and initiated treatment. This high yield suggests that pharmacy professionals are highly effective screeners for TB.

**Conclusions:** Equipped with the SwipeRx e-referral tool, pharmacy professionals can significantly contribute to TB case finding in the community, channeling patients to access free TB treatment. The use of an e-referral tool has improved the availability, efficiency and transparency of data from the point of referral in the pharmacy to referral outcome in the health facilities.

### OA-36-722-24 Improving tuberculosis preventive therapy data quality in Ethiopia

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**Background and challenges to implementation:** In 2018, the Ethiopian Federal Ministry of Health in collaboration with the U.S. Centers for Disease Control and Prevention under the President's Emergency Plan for AIDS Relief started scaling up tuberculosis (TB) preventive therapy (TPT) using a multipronged strategy. A key component was promoting the use of high-quality data to monitor progress toward TB/HIV epidemic control. However, information captured in electronic medical records (EMR) were incomplete. We report outcomes of the data quality improvement (DQI) activities conducted after the CDC facilitated monitoring and evaluation training to promote high-quality patient data for programmatic use.

**Intervention or response:** In March 2019, we collected baseline data (pre-DQI) related to key programmatic variables from EMR at 47 facilities in Addis Ababa. DQI activities (i.e., in-person trainings, implementation of standard operating procedures, mentorship, and creating a community of practice for TB/HIV providers) were undertaken in April 2019. EMR data were analyzed in January 2020 (post-DQI). A single stage cluster design was used to account for potential differences in data completeness at facility level by comparing the proportion of pre-DQI and post-DQI records with documentation for TB screening, TPT initiation, TPT completion, and viral load status P-values <0.001 were considered statistically significant.

**Results/Impact:** Our analysis included 66,760 unique pre-DQI records and 71,944 unique post-DQI records (8% increase). TB screening results captured at the last visit were 100% complete for both time periods. Documentation on TPT initiation increased 3.5 times (pre-DQI, 11,745/66,760 [18%]; post-DQI, 44,977/71,944 [63%]; p<0.001). Documentation of TPT completion

also increased 3 times (pre-DQI, 10,704 [16%]; post-DQI, 36,318 [50%]; p<0.001). Proportion of records with incomplete viral load status data decreased 9 times (pre-DQI, 59,315/66,760 [89%]; post-DQI, 7,485/71,944 [10%]; p<0.001).

**Conclusions:** DQI improved data quality and documentation for key programmatic variables. Improving data completeness is a critical step in monitoring programmatic performance and tracking progress toward TB/HIV epidemic control.

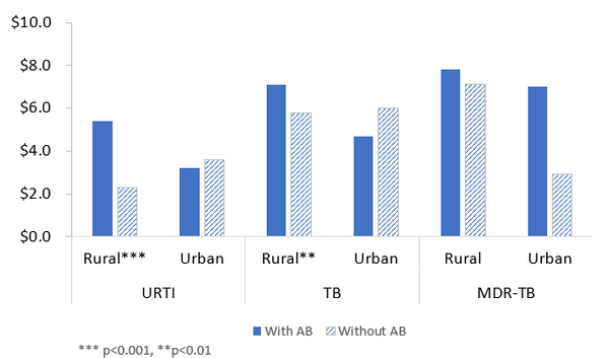
### OA-36-723-24 Treating viral infections and tuberculosis with antibiotics in Vietnam: Is there any financial benefits for community pharmacies?

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**Background:** Antibiotics are frequently used excessively, resulting in increased antibiotic resistance. A possible driver of this behaviour is the efforts by pharmacies to maximise their financial revenue. This study evaluated the costs of pharmaceutical management of viral infections and tuberculosis (TB) in four provinces of Vietnam. **Design/Methods:** We utilised simulated patient approach that involved trained actors to perform three clinical scenarios: viral upper respiratory tract infection (URTI) (n=316), TB (n=318), and multidrug-resistant TB (MDR-TB) (n=320) at private pharmacies across two Northern and two Southern provinces of Vietnam. Data on the dose, frequency, the duration of supplied medications, and the cost-per-visit were recorded. Costs were converted to 2020-\$US using the purchasing power parities for GDP-per-capita data published by the International Monetary Fund. Descriptive statistics and sensitivity analysis that used imputed cost-per-visit by pharmacists were applied.

**Results:** Antibiotics were supplied to 280 (89%) URTI patients, 253 (79.6%) and 185 (57.8%) patients with presumptive TB and MDR-TB, respectively. The median costs in treating URTI with antibiotics were significantly higher than without antibiotics. Pharmaceutical costs with antibiotics given to presumptive TB and MDR-TB patients were higher than those without antibiotics but were not significant. The pharmaceutical costs for URTI and TB, either with or without antibiotics, were significantly higher in rural areas and in the North compared to in urban areas and in the South, respectively. For example, median costs for treating URTI with antibiotics were \$7.8 [IQR \$5.2-\$11.7] in rural areas versus \$7.0 [IQR \$3.5-\$14.3] in urban areas (p<0.0001). Analysis of the imputed data showed consistent results.





[Figure. Costs of pharmaceutical treatment for URTI, TB and MDR-TB within Vietnamese private pharmacies]

**Conclusions:** Treatment of viral infections with antibiotics within private pharmacies resulted in higher costs to patients compared to treatment without antibiotics. Policies that reduce the inappropriate use of antibiotics by patients with viral illnesses, will reduce out-of-pocket expense for patients, and improve the quality of care in Vietnam.

**OA-36-724-24 Engaging private-sector drug retailers in Nigeria's effort to improve TB case identification: screening and diagnostic gaps from a two-state mystery client survey**

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**Background:** The WHO classifies Nigeria as high burden country for TB. While Nigeria's national program to fight TB has historically relied on clinical providers, drug retailers—specifically, patent and proprietary medicine vendors (PPMVs)-- are the first source of care for up to 55% of the population. and represent an untapped resource for combating TB. The USAID-funded SHOPS Plus program implemented a study to evaluate the extent that trained PPMVs appropriately identified and managed presumptive TB cases.

**Design/Methods:** The study examined the behavior of 389 PPMVs from urban areas of Lagos and Kano using a mystery client (MC) survey methodology. Two different MCs approached PPMVs: one sought treatment advice for a persistent cough, the other directly requested to purchase a 'loose' TB drug (rifampicin). Both scenarios should have prompted trained PPMVs to initiate screening and sputum collection or referral to facilitate TB diagnosis.

**Results:** In response to MCs seeking treatment advice, most PPMVs engaged in basic screening (70% confirmed cough duration of 2 weeks or longer), but only 34%

managed to initiate/recommend sputum collection. Though few (2%) PPMVs sold TB drugs in response to direct requests for them, most providers (93%), did not conduct any screening or initiate sputum collection with these clients.

Results	Scenario: Mystery client presents with a cough and fever (n=355)		Scenario: Mystery Client Directly Asks to buy a pack of Rifampicin (n=358)	
	n (%)	95% CI	n (%)	95% CI
Criteria 1: Asked about duration of cough	250 (70.4%)	(67.1%, 73.6%)	17 (4.7%)	(3.4%, 6.6%)
Asked any screening or history questions	305 (85.9%)	(83.2%, 88.3%)	26 (7.3%)	(5.6%, 9.4%)
Mean # of screening questions asked	3.4	(3.2, 3.6)	0.2	(.2, .3)
Criteria 2: Took a sputum sample or referred MC for sputum test in other facility	120 (33.8%)	(30.4%, 37.4%)	20 (5.6%)	(4.1%, 7.5%)
Referred MC elsewhere for diagnosis	13 (3.7%)	(2.5%, 5.3%)	2 (0.6%)	(0.2%, 1.4%)
Criteria 3: No sale of unnecessary antibiotics, anti-TB drugs, or steroids	159 (44.8%)	(41.2%, 48.5%)	328 (91.6%)	(89.3%, 93.4%)
Mean # of medications prescribed	1.4	(1.3, 1.5)	0.2	(.2, .3)
Successful MC management (met all 3 criteria)	76 (21.4%)	(18.5%, 24.6%)	7 (2%)	(1.2%, 3.3%)

[Table 1. Summary mystery client survey results]

**Conclusions:** Results suggest PPMVs engage in low-levels of unauthorized dispensing of TB drugs in Lagos and Kano, but also show PPMVs are missing opportunities to screen clients that do not overtly complain of cough and initiate sputum collection. Beyond the training PPMVs received, other system-level challenges could be affecting their willingness to correctly manage presumptive TB patients. Such constraints need to be identified and addressed to effectively engage PPMVs in TB response.

**OA-36-725-24 Exploring the attitudes and practices of pharmacy professionals toward dispensing NTP-provided FDCs**

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**Background:** While fixed-dose combination (FDC) drugs for tuberculosis (TB) has been recommended by the World Health Organization (WHO) as the standard treatment, Indonesia's private TB market is dominated by first-line single-formulation drugs dispensed by pharmacies. The study aims to explore pharmacy professional practices and attitudes toward dispensing National TB Program (NTP)-provided FDCs.

**Design/Methods:** We conducted a cross-sectional digital survey between February through March 2020. 404 responses were received (95% CI and 5% ME).

**Results:** 80% or more of pharmacy professionals dispensed generic first-line single-formulation drugs and 65% did not have access to NTP-provided FDCs.



Among those, 46% revealed they didn't know about the NTP-provided FDCs. Although >85% believed about the benefit of FDCs, 40% revealed that they would be hesitant to dispense NTP-provided FDCs if no financial incentives were provided. They suggested having a simplified reporting process and incorporating digital and health information tools for convenience and efficiency. Nevertheless, 92% would be willing to report NTP-provided FDCs consumption to the District Health Offices if they can dispense it and desire more education on the NTP-provided FDCs.

**Conclusions:** To make NTP-provided FDCs more available to patients at the pharmacy, we found it is essential to include retail and chain pharmacies in the District-based Public Private Mix (DPPM) framework and promoting participation among hospital and clinic pharmacies. While attitudes toward the provision of NTP FDCs were positive, financial incentives and simplification of the administrative processes may be needed for widespread participation among pharmacies. Furthermore, bringing awareness and education to pharmacies on the NTP-provided FDCs and the benefits of FDC drugs in TB treatment can engage them to make FDC drugs more available at the pharmacy.

### OA-36-726-24 Assessing antibiotic sales for presumptive and multidrug-resistant tuberculosis patients by community pharmacies in Vietnam: a standardised patients survey

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**Background and challenges to implementation:** Selling antibiotics without prescription is a driver of inappropriate antibiotic use, which is associated with treatment complications and antibiotic resistance globally.

To estimate the proportion of antibiotics sold in community pharmacies without a prescription for patients presenting with presumptive tuberculosis (TB) and presumptive multidrug-resistant tuberculosis (MDR-TB) in Vietnam, and evaluate factors associated with inappropriate sales.

**Intervention or response:** A cross-sectional standardised patients' survey was conducted among 638 mapped community pharmacies and drug counters (pharma-

cies) in forty Districts in four provinces of Vietnam. Randomly selected pharmacies were visited by a trained actor ('standardised patient') following a standardised scenario of presumptive TB and presumptive MDR-TB. Details of the encounter were recorded immediately after each visit. The data were analysed using descriptive and inferential statistics.

**Results/Impact:** Pharmacies sold non-prescribed antibiotics in 511 [80.1% (95% CI 77-83)] of 638 interactions. This included 286/318 (89.9%) standardised patients (SPs) with presumptive TB and 225/320 (70.3%) with presumptive MDR-TB. About 46.9% of SPs were given cephalosporins, quinolones (17.5%), penicillins (15.9%), macrolides (12.4%), and other antibiotics (7.3%). Among SPs with a history of MDR-TB, cephalosporins (33.6%), penicillins (19.1%), macrolides (18.3%), quinolones (16.2%) were commonly given. Fourteen encounters for presumptive TB and 17 for MDR-TB resulted in sales of the fluoroquinolone levofloxacin, which could contribute to acquired drug resistance.

Pharmacies in the Northern part of Vietnam were more likely than Southern provinces to sell antibiotics without prescription for both presumptive TB (Adj.OR=3.01, 95% CI: 1.37-6.60) and MDR-TB (Adj.OR=5.13, 95% CI: 2.94-8.96).

**Conclusions:** Despite Vietnamese law prohibiting antibiotic sales without a prescription, patients with presumptive TB and MDR TB were able to widely access to antibiotics without a prescription. Broad-spectrum antibiotics including anti-TB antibiotics for TB patients may delay appropriate TB treatment and contribute to acquire drug resistance. This study urges greater regulatory enforcement and antimicrobial stewardship to strengthen pharmacy practice.

### OA-36-727-24 The impact of patent medicine vendors in increasing tuberculosis case detection among hard-to-reach dwellers in selected districts in Nasarawa State, Nigeria

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**Background and challenges to implementation:** Despite the high burden of tuberculosis in Nigeria, case detection is generally low and even lower in hard-to-reach populations due to non-availability or inadequate formal health facilities. Studies on health-seeking behaviour of patients with chronic cough revealed that 60% of respondents seek first level care from patent medicine vendors (PMVs)—a constant feature in Nigeria's informal health sector. This study assesses the impact of PMVs in increasing TB case detection among hard-to-reach dwellers in two hard-to-reach districts in Nasarawa state, Nigeria.

**Intervention or response:** We identified twenty patent medicine vendors in collaboration with the leadership of the National Association of Patent and Proprietary Medicine Dealers (NAPPMED) in two districts, namely Nasarawa and Wamba. The 20 PMVs were trained on the identification of presumptive TB, documentation, and referral to DOTs facilities. The documentation tools and client's educational materials in the local language (Hausa) were provided. Periodic visits and phone-call follow up to PMVs were made. Bi-monthly performance reviews were held and incentives were provided based on the number of presumptive and TB cases reported. We reviewed the contribution of the PMVs to the total TB case finding between January 2018 and December 2018 in the two districts.

**Results/Impact:** In 2018, out of the total presumptive TB (3641) identified in the two districts, 1177 (32%) were from the PMVs in these hard-to-reach districts. Of all the 424 TB cases notified from these districts, 108 (25%) were diagnosed from successful referrals by the PMVs. The bacteriologic positivity rate of the presumptive TB clients referred by the PMVs was 9%.

**Conclusions:** PMVs presents a great opportunity for finding persons with tuberculosis especially among the poorest people who dwell in hard-to-reach settings. Expanding access to TB services to the informal private health care providers will contribute to closing the gaps in TB case detection in Nigeria.

## OA-37 TB and HIV potpourri

### OA-37-728-24 Depression and its associated factors in persons with multidrug-resistant tuberculosis in Myanmar

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**Background:** Depression is identified as an important potential co-morbidity in persons with TB, yet data in many settings are scarce. The present study aimed to estimate the prevalence and risk factors of depression in persons with MDR-TB in Yangon, Myanmar.

**Design/Methods:** A cross-sectional survey was conducted in MDR-TB participants, registered between January 2018 and January 2020 at Aung San MDR-TB treatment centre in Yangon, during a routine clinic follow up visit.

Patient Health Questionnaire-9 (PHQ-9) (previously validated in Myanmar for persons with chronic conditions) was used to screen for depression. Univariable and multivariable logistic regression were performed to identify associations.

**Results:** Of 732 eligible, registered persons at the study site, (not known to have transferred or died by the time of the study), 329 (45.0%) were enrolled (65.4 % male, mean (sd) age 40.0 years, ( $\pm 14.2$ ). Sixty-six percent were in continuation phase. Complete data were obtained for all variables. The prevalence of depressive symptoms (PHQ9  $\geq 10$ ) was 10.3% (95% CI: 7.3-14.1) and other co-morbid conditions including moderate or severe malnutrition (BMI $<17.0$  kg/m<sup>2</sup>) was 33.7%; HIV 12.2% and reported diabetes 16.1%. In multivariable analysis, financial hardship as a result of MDR-TB symptoms/treatment (aOR=2.63, 95% CI: 1.12-6.67), female sex (aOR=2.09, 95% CI: 0.94-4.65), suffering one or more current respiratory symptoms (aOR=6.72, 95% CI: 2.41-18.76), high education level (aOR=4.26, 95% CI: 1.70-10.70), and reported diabetes (aOR=3.05, 95% CI: 1.16-7.99) were independently associated with increased risk of depressive symptoms.

**Conclusions:** Symptoms of depression are common in persons with MDR-TB in Myanmar. It is recommended to implement/strengthen regular follow up assessment of depression in persons with MDR-TB by health care professionals using simple, standardized, short, validated tools.

### OA-37-729-24 Enteropathogens negatively impact antimycobacterial drug pharmacokinetics in children from rural Tanzania

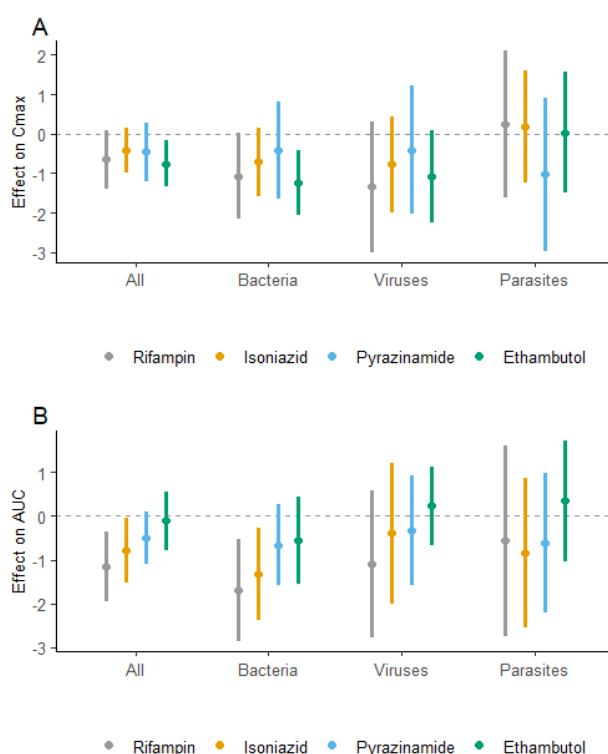
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**Background:** Adequate drug exposure is critical for successful tuberculosis (TB) therapy, yet malnourished children may have poor attainment of pharmacokinetic targets. As enteropathy is prevalent in TB-endemic areas and has been shown to impair absorption, enteropathogen burden may negatively impact antimycobacterial pharmacokinetics.

**Design/Methods:** Among children undergoing TB treatment with first-line therapy in rural Tanzania, we quantified enteropathogen burden using multiplex stool polymerase chain reaction. Serum was collected during

the dosing interval to determine peak ( $C_{max}$ ) and total area under the concentration curve ( $AUC_{0-24}$ ). Enteropathogen burden was compared to pharmacokinetic measurements using bivariate and multivariate regression.

**Results:** 45 children undergoing TB treatment were enrolled and 38 (84.4%) had moderate or severe malnutrition. A mean of 2.1 enteropathogens were detected per participant; notably *Clostridioides difficile* was detected in 23 participants (51%). In controlled comparisons, summative enteropathogen burden was negatively associated with rifampin  $AUC_{0-24}$  ( $p = 0.008$ ), isoniazid  $AUC_{0-24}$  ( $p = 0.04$ ), and ethambutol  $C_{max}$  ( $p = 0.02$ ) in those with gastrointestinal symptoms.



[Figure.]

**Conclusions:** Tanzanian children undergoing TB treatment rarely attained pharmacokinetic targets, enteropathogen carriage was common, and enteropathogen burden was as a risk factor for sub-target antimycobacterial drug concentrations.

## OA-37-730-24 Finding the missing cases One-by-Two: testing contacts of people with presumptive TB to close TB and HIV case-finding gaps in the Democratic Republic of Congo

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**Background and challenges to implementation:** The Democratic Republic of the Congo is continuing to make progress towards in tuberculosis (TB) and HIV case finding goals—2018 data indicates a 64% TB case detection rate and an estimated 63% of people living with HIV (PLHIV) diagnosed. However, missing cases continue to fuel the dual epidemic, necessitating novel community-based approaches to proactively reach individuals not accessing services at healthcare settings.

**Intervention or response:** The USAID-funded Integrated HIV/AIDS Project in Haut Katanga (IHAP-HK) piloted the One-by-Two approach at two TB treatment centers (Kenya General Reference Hospital; Abbé Delbeck Health Facility), whereby an index client with presumptive TB is tested for HIV and also counseled to bring two household contacts or family members exhibiting similar symptoms (e.g. cough, fever, night sweats) to their next appointment. Contacts are first tested for HIV, following an HIV risk assessment, then referred to the laboratory for TB screening. Individuals confirmed positive are then initiated on anti-TB and/or antiretroviral therapy.

We analyzed 13 months (February 2019-March 2020) of programmatic data using descriptive statistics.

**Results/Impact:** When all 35 index clients and 58 contacts were tested, we identified 43 people with confirmed TB and 58 PLHIV, all first-time HIV testers (see table). If we only tested the 43 people with confirmed TB, we would have identified 26 PLHIV, thus missing 32 PLHIV. Conversely, if we only screened the 58 PLHIV for TB, we would have identified 26 people with TB and missed 17.

	Index client with presumptive TB (n=35)	Contact (n=58)	Total (n=93)
People with confirmed active TB	25 (71%)	18 (31%)	43 (46%)
PLHIV	30 (86%)	28 (48%)	58 (62%)
TB/HIV co-infected people	21 (60%)	5 (9%)	26 (28%)

[Table.]

**Conclusions:** The One-by-Two approach identified 18 more people with confirmed TB and 32 more PLHIV without requiring additional outreach by healthcare

providers, highlighting this as an efficient tracing strategy to accelerate diagnosis of individuals living with TB and/or HIV currently missed by outreach efforts. This approach should be rapidly extended to other TB clinics in high TB/HIV burden settings to diagnose hard-to-reach individuals and link them to treatment.

### OA-37-731-24 Integration of LF-LAM into advanced HIV disease management package: early implementation lessons from Uganda

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**Background and challenges to implementation:** An early program evaluation on Implementation of LF-LAM was conducted in October 2018 to guide countrywide scale up. This evaluation revealed sub-optimal utilization of LF-LAM test. The major implementation challenges identified were; lack of supportive structures such as CD4 cell testing, LF-LAM diagnostic algorithm, recording and reporting procedures and stock management procedures.

**Intervention or response:** A Technical Working Committee (TWC) for Advanced HIV Disease (AHD) comprising of members from the National TB and Leprosy Program and AIDS Control Program was instituted. The TWC developed a tool kit and an implementation plan for AHD management addressing the above hindrances.

Specifically, the TWC mapped out high volume health facilities with the capacity to perform CD4, LF-LAM and CRAG testing, procured and distributed reagents for CD4 testing, availed LF-LAM diagnostic algorithm, recording and reporting procedures and stock management procedures to all AHD sites. National and sub-national level key stake holders' orientation meetings as well as training of health workers was conducted across the 12 health regions in Uganda.

**Results/Impact:** We evaluated the performance of LF-LAM across the AHD implementation sites six months before (Jan-Jun 2019) and after (July-Dec 2019) the interventions at 914 health facilities across the country. A total of 12,070 (July-Dec 2019) and 8,597 (Jan-Jun 2019) PLHIV had a CD4<200 cells/mm respectively. The utilization of LF-LAM in July-Sep 2019 was 51% (6,196/12,070) up from 40% (3,453/8,597) in Jan-Jun

2019. The overall TB cases diagnosed among PLHIV increased from 556 to 1,388 during the implementation period.

**Conclusions:** The integration of LF-LAM into AHD management package led to an improvement in its utilization and TB yield. We recommend collaborative efforts in the implementation of LF-LAM as integral part of AHD package by the joint TB and HIV/AIDS National Programs so as to ensure its optimal performance.

### OA-37-732-24 Determining the prevalence of tuberculosis in emergency departments in the Eastern Cape region of South Africa and the utility of the WHO TB screening tool

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**Background:** South Africa faces a significant tuberculosis (TB) burden complicated by high rates of HIV-TB co-infection. Within South Africa, emergency departments (ED) serve an important role screening for TB patients. This study aims to determine the prevalence of TB in the ED and the effectiveness of the World Health Organization (WHO) TB screening tool.

**Design/Methods:** This is a cross-sectional observational study. All patients presenting to the Livingstone Hospital (Port Elizabeth) ED from June 4, 2018 – July 15, 2018, over age 18, and able to consent were recruited to participate. All patients were administered the WHO TB screening questions, provided a point-of-care HIV test, and underwent demographic data collection. Patients were followed for one-year and tracked within the National Health Laboratory Service (NHLS) database to determine TB status using laboratory testing.

**Results:** Over the study period, 790 patients were enrolled. Overall, 121 (15.3%) patients were TB-positive, with 46 (38.0%) diagnosed after presenting to the ED and 75 (62.0%) with previous TB history determined by self-report or confirmed laboratory testing. A greater proportion of the TB-positive population was HIV-positive (60, 49.6%) compared to the TB-negative population (64, 24.8%). TB-positive individuals presented to the ED with a chief complaint of shortness of breath (SOB) (22, 18.2%) more than the TB-negative population (27, 10.5%).

The WHO tool was effective in identifying positive TB patients but had poor sensitivity (46.5%) and specificity (62.5%). A multiple logistic regression, controlled for age and sex, showed HIV status (OR 2.81,  $p < 0.001$ ) and SOB (OR 2.19,  $p < 0.05$ ) to be significant predictors of TB positivity. Adding positive HIV status and a presenting complaint of SOB increased sensitivity to 78.3%.

**Background and challenges to implementation:** South Africa faces a significant tuberculosis (TB) burden complicated by high rates of HIV-TB co-infection. Within South Africa, emergency departments (ED) serve an important role screening for TB patients. This study aims to determine the prevalence of TB in the ED and the effectiveness of the World Health Organization (WHO) TB screening tool.

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**Conclusions:** EDs in South Africa face a high burden of TB. While WHO screening guidelines identify some of these patients, including routine HIV testing in the ED could significantly impact the number of diagnoses made.

### OA-37-733-24 An in vitro intracellular Mycobacterium tuberculosis and HIV-1 co-infection model suitable for imaging-based platforms

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**Background:** *Mycobacterium tuberculosis* (*Mtb*) is an obligate, intracellular bacillus, causing the human disease Tuberculosis (TB). The Human Immunodeficiency Virus (HIV-1) is a lentivirus that causes AIDS (Acquired Immune Deficiency Syndrome) in humans. Both diseases are among the leading causes of mortality worldwide. *Mtb* and HIV-1 are classed as hazard group 3 (HG3) pathogens by the UK Advisory Committee for Dangerous Pathogens, as such they are worked with and stored in containment level 3 (CL3) laboratories. The aim of this work was to develop a safe methodology to co-infect macrophage cells with *Mtb* and HIV-1 suitable for UK CL3 laboratories to monitor pathogen interactions and for drug screening purposes.

**Design/Methods:** We utilised multiple fluorescence-based methodologies to quantify the co-infection. By employing genetically modified *Mtb* and HIV-1, both carrying fluorescent molecules, we used flow cytometry and microscopy to study levels of infection in the presence or absence of drugs. Much optimisation was required in the development of these methodologies, from cell number, MOI and viral load.

**Results:** Co-infections were quantified and monitored using different approaches: fluorometry, luciferase, confocal microscopy and flow cytometry. Co-infections were performed in presence or absence of antiretroviral (Efavirenz [EFV]) and/or a first-line TB antibiotic (Rifampicin [RIF]). EFV completely inhibited HIV-1 infection in a single and co-infection setting, and interestingly RIF also reduced the HIV-1 infection rate by 12%. RIF reduced *Mtb* viability by more than 50% in a single infection and by 57% in a co-infection setting. The combination of drugs and presence of both virus and bacteria significantly affected infection rates and pathogen viability.

**Conclusions:** We have successfully developed a methodology to co-infect THP-1 cells with HIV-1 pseudo virus particles and *Mtb*, ensuring host cell viability. Our method can be easily applied to address biological questions concerning the HIV-1/*Mtb* co-infection process as well as be used for drug screening.

### OA-37-734-24 Impact of integrating mental health services within existing tuberculosis treatment facilities

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**Background:** Tuberculosis (TB) has a high level of comorbidity with depression/anxiety; and poor mental health can adversely affect TB treatment adherence and completion.

This study aims to evaluate whether the integration of counseling services within TB treatment programs can help reduce symptoms of depression/anxiety and improve TB treatment completion.

**Design/Methods:** An Integrated Practice Unit (IPU) model was used to embed mental health services within existing TB treatment programs.

IPUs were set up within six TB facilities across public and private hospital settings in Karachi, Pakistan. The IPU provided screening for depression and anxiety for patients seeking treatment for drug susceptible TB at the study sites. Patients who were symptomatic for depression or anxiety were offered a mental health intervention comprised of 4-6 counseling sessions provided by

a trained lay-counselor, and were reassessed post intervention. Changes in reported levels of depression and anxiety were measured between baseline and end-line assessments. Rates of TB treatment completion were measured between those who completed the mental health intervention and those who did not.

**Results:** Between February 2017-June 2018, 3500 TB patients were screened for depression/anxiety (M=1795, F=1705), mean age = 34.7 years, SD (15.6). Of those screened, 30 % (n=1057) were symptomatic for depression and anxiety. 1012 were enrolled for a mental health intervention and received at least 1 counselling session. 522 (51.5%) completed the intervention and reported no symptoms at end-line. Symptomatic patients who completed at least 4 counselling sessions had higher rates of tuberculosis treatment completion than those who did not (92.9% versus 75.1%;  $p < 0.0001$ ).

**Conclusions:** Our results suggest that mental health counselling can reduce symptoms of depression and anxiety among TB patients and significantly improve TB treatment completion, making a strong case for the integration of mental health services with TB programs.

## OA-38 Diagnostic assays quality and accuracy

### OA-38-735-24 Diagnostic accuracy of the Molbio Truenat TB and RIF-resistance assays in the intended setting of use

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**Background:** Bringing sensitive tuberculosis (TB) diagnosis closer to patients is a key global TB control priority. Molbio Diagnostics have developed point-of-care Truenat assays that utilize chip-based real-time micro-PCR for detection of TB and rifampicin (RIF)-resistance. We report results of the clinical evaluation of the Truenat MTB, Truenat MTB Plus and MTB-RIF Dx assays.

**Design/Methods:** We conducted a prospective multi-centre study at 19 microscopy centres and 7 reference laboratories in 4 countries to determine the diagnostic accuracy of the Truenat assays using culture as the reference standard. We report results from Molbio assays performed at microscopy centres as well as results from head-to-head testing with Xpert and Ultra as comparator tests, performed in reference laboratories.

**Results:** 1,925 adults under evaluation for TB were included. Culture results were available for 1,654 participants at the time of this analysis; proportion TB positive was 24% (n=393), with 16% (n=62) of TB patients being RIF-resistant. In microscopy centres, sensitivity of Truenat MTB was 73% [95%CI 68, 78], and sensitivity of Truenat MTB Plus was 80% [95%CI 75, 84] (n=1,336); among smear-negative specimens, sensitivities were 37% [95%CI 27, 48] and 46% [95%CI 36, 57], respectively. The specificities of Truenat MTB and MTB Plus was 98% [95%CI 97, 99], and 97% [95%CI 95, 97], respectively. In raw sputa tested in reference laboratories, the sensitivities of Truenat MTB, Xpert, Truenat MTB Plus, and Ultra assays were 84%, 85%, 87% and 96%, respectively; specificities were 97%, 97%, 95% and 97%, respectively. For RIF-resistance detection, the sensitivity of the Truenat MTB-RIF assay was 84% [95%CI 72, 92], and specificity was 97% [95%CI 95, 99], comparable to performance of both Xpert and Ultra tests.

**Conclusions:** Truenat MTB and MTB Plus assays have comparable accuracy to Xpert and Ultra and can be performed in microscopy centres and primary health centres.

### OA-38-736-24 SILVAMP-LAM for the diagnosis of childhood pulmonary tuberculosis in Uganda

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**Background:** Urine lipoarabinomannan (LAM) testing provides a non-sputum, point-of-care assay for pulmonary TB, but current tests have not performed well in children. We compared the performance of the new FUJIFILM SILVAMP TB LAM (SILVAMP-LAM) to Alere Determine TB LAM Ag (LF-LAM) and sputum smear microscopy for pediatric TB diagnosis.

**Design/Methods:** We consecutively enrolled children <15 years old who were being evaluated for pulmonary TB in Kampala, Uganda. All children had a complete TB evaluation, including tuberculin skin testing, chest x-ray, and respiratory specimen collection for Xpert MTB/RIF Ultra, smear microscopy, and liquid and solid culture. SILVAMP-LAM and LF-LAM testing were performed on urine obtained at baseline. We calculated and compared the sensitivity and specificity of the two LAM tests in reference to NIH consensus definitions of Confirmed vs. Unlikely TB, and yield in children with Unconfirmed TB.

**Results:** We included 71 children, among whom median age was 5 years (IQR 2.2-8), 46% were female, 11% were HIV-positive (median CD4 cell count 853 cells/uL, IQR 625-1272), 61% were underweight and 25 (35%) had Confirmed TB. The sensitivity of SILVAMP-LAM was 56% (95% CI 34.9-75.6), compared to 24% (95% CI 9.4-45.1) in LF-LAM (difference +32%, 95% CI 9.7-54.3,  $p=0.01$ ). The specificity of SILVAMP-LAM was 94.3% (95% CI 80.8-99.3) versus 100% (95% CI 90-100) for LF-LAM (difference -5.7%, 95% CI -16.3 to +4.8,  $p=0.5$ ). SILVAMP-LAM was more sensitive than sputum smear microscopy (36%, 95% CI 18-57.5), although results were not statistically significant (difference +20%, 95% CI -3.2 to +43.2,  $p=0.13$ ). SILVAMP-LAM was positive in 5/11 (45%) children with Unconfirmed TB.

**Conclusions:** SILVAMP-LAM had more than double the sensitivity of LF-LAM, and detected a large proportion of Unconfirmed TB cases. SILVAMP-LAM should be prioritized as a tool for pediatric TB diagnosis, especially when sputum-based testing is not possible.

### OA-38-737-24 Diagnostic accuracy of the Xpert MTB/XDR assay for isoniazid and second-line drug resistance detection

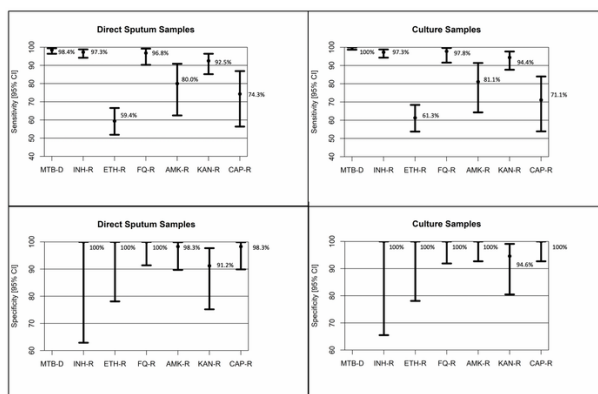
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**Background:** The development and implementation of rapid molecular diagnostics for tuberculosis (TB) drug-susceptibility testing (DST) is critical to inform patient treatment and to prevent the emergence and spread of resistance. We report preliminary results from a diagnostic accuracy study of the Xpert MTB/XDR assay (Cepheid, USA) for detecting resistance to isoniazid (INH), ethionamide (ETH), fluoroquinolones (FQs),

and second-line injectables (amikacin (AMK), kanamycin (KAN), and capreomycin (CAP)), and to determine non-determinate rates.

**Design/Methods:** Patients with microbiological confirmation of *M. tuberculosis* and at least one risk factor for drug-resistant TB were prospectively enrolled between four clinical sites in Moldova, India and South Africa. Xpert MTB/XDR testing on both direct sputum and culture were evaluated against a composite reference standard of phenotypic DST and whole genome sequencing (WGS).

**Results:** We analyzed preliminary data from a total of 381 patients (of 760 planned final sample size) in April 2020. The Xpert MTB/XDR assay demonstrated excellent performance for the detection of INH, FQ, AMK, KAN and CAP resistance, regardless of whether the assay was performed directly on sputum samples or cultured isolates (Figure). Xpert MTB/XDR non-determinate rates were 2.65% when performed directly on patient sputum samples. No notable assay performance differences were identified by site, smear result, HIV-infection status or patient pre-treatment status at this time.



[Figure.]

**Conclusions:** This study suggests Xpert MTB/XDR sensitivity is highly accurate for INH (97%), FQ (97%), KAN (93%), AMK (80%), and CAP (74%) resistance detection in relevant clinical settings. Specificity was >98% for all targets except KAN (91%), although estimates for accuracy for some targets were uncertain due to the small sample size in this preliminary analysis; updated results based on final sample size will be presented at the meeting.



**OA-38-738-24 The diagnostic accuracy of Xpert MTB/RIF Ultra for childhood pulmonary tuberculosis in Uganda**

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**Background:** Sputum Xpert MTB/RIF Ultra (Xpert Ultra) has improved sensitivity in adults with smear-negative TB. Children have paucibacillary TB and may benefit from Xpert Ultra, but there have been no prospective studies of its diagnostic accuracy in a pediatric population.

**Design/Methods:** We conducted a diagnostic study among children (<15 years) presenting for evaluation of pulmonary TB in Kampala, Uganda. We completed a clinical exam and obtained respiratory specimens (sputum, gastric, or nasopharyngeal aspirate) for Xpert Ultra, solid, and liquid TB culture. We calculated the sensitivity and specificity of Xpert Ultra among children with confirmed (i.e., culture-positive TB) and unlikely TB, respectively, per NIH consensus definitions. We also calculated the yield of Xpert Ultra in children with unconfirmed TB.

**Results:** We consecutively enrolled 200 children, of whom 30 (15%) had confirmed TB, 68 (34%) had unconfirmed TB and 102 (51%) had unlikely TB. The median age at enrollment was 3.9 years (IQR 1.5-7), 51% of participants were male, 11% were HIV-positive (median CD4 cell count 736 cells/ul, IQR 394-981), and 60% were underweight. Overall, the sensitivity of Xpert Ultra was 70% (95% CI 50.6-85.3) and specificity was 100% (95% CI 96.4-100). There was no significant difference in sensitivity by age category, weight category, or specimen type (gastric/nasopharyngeal aspirates versus expectorated/induced sputum). Xpert Ultra was positive in 11 of 68 (16.2%, 95% CI 9.1-27.1) children with unconfirmed TB. Xpert Ultra “trace” positive results accounted for 25% (8/32, none with HIV infection) of all positive results, of which the majority (6/8, 75%) were classified as unconfirmed TB.

**Conclusions:** Xpert Ultra is a useful tool for diagnosing pulmonary TB in children. Trace findings contributed to a quarter of positive results and may play an important role in identifying culture-negative cases.

**OA-38-739-24 External Quality Assurance of the Xpert MTB/RIF Ultra assay using Mycobacterium tuberculosis isolates inactivated in PrimeStore® Molecular Transport Medium: a safe, simple and local solution**

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**Background:** A robust External Quality Assurance (EQA) program is essential to ensure accurate results using the Xpert MTB/RIF Ultra assay. PrimeStore® Molecular Transport Medium (MTM) inactivates pathogens and stabilizes nucleic acids for molecular testing. Samples can be safely transported and stored at ambient temperatures for extended periods and do not require any additional processing steps before testing. We tested the idea that *Mycobacterium tuberculosis* isolates inactivated in PrimeStore® MTM could provide a safe, simple, and locally-produced method for EQA of Xpert Ultra.

**Design/Methods:** Four mycobacterial isolates grown in MGIT liquid culture [MTB drug-sensitive, MTB RIF-resistant, MTB INH-resistant, and non-tuberculous mycobacterium (NTM)] were inactivated in PrimeStore® MTM, per manufacturer’s instructions. 1mL aliquots were stored at ambient temperature for periodic Xpert Ultra testing over one year to assess stability. Xpert testing was performed, per manufacturer’s instructions, by mixing 1mL EQA aliquot with 2mL Xpert reagent buffer, then loading 2mL of the mixture into an Xpert Ultra cartridge. Cultures were inoculated to confirm the material was non-infectious. PrimeStore® MTM was provided by Longhorn Vaccines & Diagnostics, LLC.

**Results:** Xpert testing was performed at weeks 0, 2, 4, 6, 8, and 10. Cycle threshold (Ct), level of positivity, and RIF-resistance were similar at all time-points: 1. MTB isolates were always ‘MTB detected High or Medium’, 2. Drug-sensitive and INH-resistant isolates were always ‘RIF-resistance not detected’ (RRND), 3. RIF-resistant isolate was always ‘RIF-resistance detected’ (RRD), and 4. NTM isolate was always ‘MTB Not Detected’. Week 10 results for the MTB isolates are shown in Table 1. Culture results pending.

Isolate	Xpert result	SPC	Probes (Ct)				
			IS1081-IS6110	rpoB1	rpoB2	rpoB3	rpoB4
MTB drug-sens	High-RRND	26.8	16.1	18.4	18.3	19.8	20.7
MTB RIF-resist	Medium-RRD	27.1	16.3	18.9	19.0	26.1	22.4
MTB INH-resist	Medium-RRND	30.9	16.2	18.6	18.6	19.8	23.0

Table 1: Xpert Ultra Results for MTB in PrimeStore® MTM (Week 10)

**Conclusions:** *Mycobacterium tuberculosis* isolates inactivated in PrimeStore® MTM and stored at ambient temperature gave consistent results in the Xpert Ultra assay through the first 10 weeks. This system could serve as the basis for a safe, simple, and locally-produced EQA program for Xpert Ultra and other molecular assays.

### OA-38-740-24 Combination of Xpert MTB/RIF and Determine TB LAM assay improves the diagnosis of extrapulmonary tuberculosis in Ethiopia

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**Background:** Ethiopia is one of the high burden countries for extrapulmonary tuberculosis (EPTB); however, the prompt diagnosis of EPTB remains challenging. This study is aimed to evaluate the diagnostic performance of Xpert MTB/RIF and Determine TB LAM assay (LAM) for the prompt diagnosis of EPTB in Ethiopia.

**Design/Methods:** A total of 147 presumptive EPTB patients, including 23 HIV positive participants were included. Extra-pulmonary samples were collected from all presumptive cases and examined using fluorescent microscopy, Xpert MTB/RIF and culture. Additional urine samples were also collected from 126 participants and were tested by LAM test. The sensitivity and specificity of Xpert and LAM tests were calculated by comparing with a composite reference standard (CRS), which comprises smear microscopy, culture and response to empirical anti-TB treatment.

**Results:** Of 147 patients, 23 (15.7%) were confirmed TB cases (culture-positive), 14 (9.5%) were probable TB (clinically, radiologically or cytologically positive and received anti-TB with good response), and 110 (74.8%) were classified as “non-TB” cases because of no evidence for TB. The overall sensitivity of Xpert MTB/RIF was 43.2% with the highest sensitivity for abscess specimen (85.7%) and lower sensitivity for pleural fluid (14.2%) with 100% specificity for all specimen types. The sensitivity and specificity of LAM test were 30.6% and 93.3%, respectively with the highest sensitivity for HIV co-infected participants (66.7%). The combination of Xpert MTB/RIF and LAM test detected 61.1% of all EPTB participants and 83.3% of HIV co-infected TB cases.

**Conclusions:** The Xpert MTB/RIF sensitivity varied across the different specimen types and Determine TB LAM test has low sensitivity for EPTB diagnosis. However, the combination of Xpert MTB/RIF and LAM could improve the sensitivity of EPTB diagnosis particularly in high TB and HIV endemic countries.

### OA-38-741-24 Comparative analytical evaluation of four centralized platforms for the detection of *M. tuberculosis* complex and detection of resistance to rifampicin and isoniazid

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**Background:** Failure to rapidly identify drug resistant tuberculosis (TB) increases the risk of patient mismanagement, the amplification of drug resistance and ongoing transmission. We generated comparative analytical data for four fully automated assays for detection of TB and multi-drug resistant (MDR) TB: Abbott RealTime MTB and MTB RIF/INH (Abbott), Hain Lifescience FluoroType® MTBDR (Hain), BD MAX™ MDR-TB (BD) and Roche cobas® MTB and MTB-RIF/INH (Roche). We included Xpert MTB/RIF (Xpert) and GenoType MTBDR<sup>plus</sup> as comparators for TB detection and for drug resistance detection, respectively.

**Design/Methods:** We assessed analytical sensitivity for the detection of *Mycobacterium tuberculosis* complex using inactivated strains (*M. tuberculosis* H37Rv and *M. bovis*) spiked into TB-negative sputa and computed the 95% limit of detection (LoD<sub>95</sub>).

We also assessed the accuracy for the rifampicin and isoniazid resistance detection using a set of 20 well characterized *M. tuberculosis* strains from the FIND biorepository that include high-confidence mutations responsible for >85% of first-line resistance mechanisms globally.

**Results:** For H37Rv and *M. bovis*, respectively, we measured LoD<sub>95</sub> values of 3,781 and 2,926 (Xpert); 322 and 2,182 (Abbott); 826 and 4,301 (BD); 10,398 and 23,139 (Hain); 2,416 and 2,136 (Roche) genomes/mL. Assays targeting multi-copy genes or gene targets (Abbott, BD and Roche) showed increased analytical sensitivity compared to Xpert. Quantification of the panel by quantitative real-time PCR (and not culture) prevents the determination of a precise LoD<sub>95</sub> and results reported here can only be interpreted for comparison purposes. All assays showed similar accuracy to GenoType MTBDR<sup>plus</sup> for the detection of rifampicin and isoniazid resistance.

**Conclusions:** The data from this analytical study suggest that Abbott, BD and Roche have similar performance to Xpert for identifying *M. tuberculosis*, with Hain being less sensitive. The clinical impact of the decreased sensitivity remains to be determined. All four assays compared well to WHO-recommended molecular MDR-TB assays.

## OA-40 Health and well-being post-TB

### OA-40-742-24 Comorbidities and all-cause mortality post tuberculosis treatment: a retrospective cohort study of patients previously treated with second-line tuberculosis drugs in Georgia

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**Background:** Little is known about the impact of pre-existing comorbidities on post-tuberculosis (TB) mortality rates. We aimed to determine the relationship between pre-existing comorbidities (including hyperglycemia, hepatitis-C virus [HCV], and human immunodeficiency virus [HIV]) with rates of all-cause post-TB mortality.

**Design/Methods:** We conducted a retrospective cohort study among patients treated for TB in the country of Georgia during 2009-2017. Eligible participants were >15years with newly diagnosed laboratory-confirmed pulmonary TB who received second-line treatment. Exposures included hyperglycemia (determined by fasting blood glucose level and/or previous diabetes diagnosis), HCV, and HIV serologic status. The outcome was all-cause mortality observed after TB treatment. Post-treatment mortality was determined (through November 2019) from the Georgia National Death Registry. We estimated hazard rate ratios (HR) and 95% confidence intervals (CI) of all-cause mortality among participants with and without pre-existing comorbidities using cause-specific hazard regression.

**Results:** Among 1416 eligible patients, 1019 had vital status determined and were included in analyses. Overall, 32 (3.1%) participants died during treatment and 84 (8.2%) died after TB treatment. Among those who died post-TB treatment, median time to death was 20.5 months (IQR 7.0–39.0) after TB treatment. Post-TB mortality rate (per 1000 person-years) among participants with hyperglycemia was 23.1 (95% CI 15.8–34.0), 24.3 (95% CI 15.1–39.1) among participants with HCV, and 69.8 (95% CI 36.3–134.1) among participants with HIV co-infection compared to 13.0 (95% CI 9.43–17.6) among those without hyperglycemia, HCV or HIV co-infection. Adjusting for age, gender, cavitory disease, and drug-resistance profile, hazard rates of mortality post-TB treatment were higher among participants with hyperglycemia (adjusted HR[aHR] 1.22, 95% CI 0.67–2.23), HCV (aHR 1.15, 95% CI 0.59–2.22), or HIV co-infection (aHR 3.49, 95% CI 1.20–10.20) compared to those without.

**Conclusions:** In our cohort, post-TB mortality occurred most commonly in the first three years after TB treatment ended. Additional post-TB care/follow-up may reduce rates of death post-TB treatment.

### OA-40-743-24 TB Sequel: characteristics of a TB cohort at treatment initiation in four African countries

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**Background:** Tuberculosis (TB) is a global health emergency with little known about the long-term sequelae. Accumulating evidence indicates that pulmonary function is already markedly impaired at the time of TB diagnosis. TB Sequel is a prospective and multi-country (Mozambique, South Africa (SA), Tanzania and The Gambia) cohort study, which aims to advance the understanding of the evolution and characteristics of long-term pulmonary impairment after TB and the role of clinical, microbiological, immunological and socio-economic risk factors.

**Design/Methods:** GeneXpert-positive participants are enrolled at the time of TB diagnosis and followed up for at least two years. Anti-TB treatment is provided through local NTP clinics. At the baseline visit, the following data are collected: clinical (ECG, spirometry, chest x-ray, etc.) and microbiological data (strain type, drug-resistance etc.), data on risk behaviour and comorbidities, demographic and socio-economic variables, as well as biological samples (sputum, urine and blood). The study is ongoing, and the preliminary results provide an overview of the TB cohort's characteristics at enrolment.

**Results:** A total of 1446 patients were enrolled into the study between 2017 and 2019. Among them, 34.8% females and 65.2% males with a mean age of 36 (SD 11.1). A total of 160 (11.3%) participants had previous TB episodes; 512 (41.2%) were HIV positive; and 210 (14.7%) were current smokers. A total of 586 valid spirometry results were obtained between baseline and two weeks of anti-TB treatment, of which 22% were normal, 58.5% showed restriction ventilation pattern, 14.4% mixed and 5.1% obstruction. The highest percentage of abnormal spirometry results was seen in The Gambia – 88.8%, and the lowest in SA – 65.2%, using GLI prediction equations for “Others”.

**Conclusions:** TB Sequel is an integral part of an overall strategy to fill a knowledge gap on the diagnosis, prevention and treatment of long-term pulmonary impairment after TB.

### OA-40-744-24 Lung function post-TB in Malawian adults: a 3 year cohort study

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**Background:** Post-Tuberculosis lung disease (PTLD) is increasingly recognised as an important consequence of pulmonary TB (PTB), although severity or prevalence estimates are uncertain, particularly in the medium-term. We present symptoms and lung function data of patients until 3 years after completion of TB treatment.

**Design/Methods:** Adult patients completing treatment for their first episode of PTB in Blantyre, Malawi were recruited. Questionnaire, clinical (including retreatment and mortality) and spirometry data were collected over 3 years of follow up. A linear mixed effects model was used to estimate the adjusted annual change in FEV1. A random intercept term on individual was used to account for repeated measures.

**Results:** Of 405 participants recruited at baseline, 308 were followed up. At the 2 year follow up visit, 212 (66.5%) were male and the median age was 35.3 years.

Of the 405 participants, 23 (5.7%) died, of whom 11 (47.8%) died in year 1. TB retreatment was initiated in 16 (4.0%) participants, mostly (15 (94.0%)) during year 1. Mean FEV1 was 2.55L (SD 0.65) and 2.54L (SD 0.65) at baseline and 3 years, respectively. Obstructive lung function was seen in 14.4% and 15.3% of participants at baseline and 3 years, respectively. Low FVC was seen in 20.7% and 13.2% of participants at baseline and 3 years, respectively. The adjusted estimate of annual change in FEV1 from the mixed effects model was 0.0026L (95% CI -0.0054, 0.010).

**Conclusions:** We found a substantial burden of PTLD among study participants with little change in FEV1 but a marked improvement in FVC over the 3-year period. Clinically- and cost-effective interventions are needed to reduce the burden of PTLD.

### OA-40-745-24 Risk factors associated to recurrent TB: a systematic review and meta-analysis

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**Background:** Recurrent tuberculosis (TB) frequency and proportion of reinfections and relapses vary in different settings. These differences may be determined by factors that predispose to either reinfection or relapse. We aimed to identify and pool risk factors for developing recurrence according different exposures.

**Design/Methods:** We searched Medline, Cochrane, LILACS and SciELO for cohort studies, case control studies and clinical trials published from January 1980 until October 2019 in English, Spanish and French. We selected studies that assessed factors associated to recurrent TB, relapses and reinfections.

We extracted summary measures, relative risk (RR), odds ratio (OR), hazard ratio (HR) and incidence rate ratio (IRR). We considered HR, IRR and OR to accurately approximate RR and directly used the extracted measures in a random effects meta-analysis performed with RStudio Version 1.1.463. Random effects meta-analysis was performed with RStudio Version 1.1.463. We tested for heterogeneity with the I<sup>2</sup> statistic. (PROSPERO number: CRD42018077867).

**Results:** Out of 157 studies on recurrent TB, 31 assessed risk factors for recurrence. Out of 39 studies that differentiated relapses from reinfections, 13 assessed risk factors for either of the two scenarios and seven assessed risk factors for both. The table shows pooled RR, 95% confidence intervals and I<sup>2</sup> statistics.

RISK FACTOR	n	RECURRENCE RR 95% CI	I <sup>2</sup> (%)	n	RELAPSE RR 95% CI	I <sup>2</sup> (%)	n	REINFECTION RR 95% CI	I <sup>2</sup> (%)
HIV infection	21	2.49 [1.88; 3.29]	64.60	10	0.87 [0.6-1.28]	31.00	11	4.64 [2.00; 10.74]	50.90
Male	18	1.40 [1.23; 1.60]	46.30	4	1.45 [0.86; 2.43]	56.70	3	2.29 [0.48; 10.85]	94.10
MDR resistance	2	5.89 [1.74; 19.90]	82.00	2	6.59 [1.97; 22.06]	76.50	2	1.57 [0.31; 7.77]	59.30
Cavitary lesions	12	1.48 [1.06; 2.07]	52.90	2	1.91 [1.24; 2.95]	0.00	2	1.49 [0.86; 2.60]	14.30
Any drug resistance	8	2.42 [1.10; 5.32]	82.60	2	2.67 [0.31; 22.95]	84.60	-	-	-
Sputum smear positive	2	1.23 [0.86; 1.75]	0.00	2	1.32 [0.74; 2.34]	0.00	2	5.85 [0.59; 57.86]	70.30
Diabetes mellitus	8	1.57 [0.92; 2.67]	75.50	2	1.70 [1.14; 2.55]	0.00	1	7.71 [3.33; 15.2]	-
Smoking	15	2.33 [1.61; 3.36]	79.50	1	2.86 [1.42; 5.75]	-	0	-	-
Alcohol consumption	13	1.68 [1.17; 2.40]	77.40	0	-	-	0	-	-

[Table 1: Risk factors for recurrent TB, RR relative risk, n=number of studies

Missing values due to insufficient data for meta-analysis.]

**Conclusions:** The main risk factors substantially differed by scenario: MDR resistance, HIV, any drug resistance and smoking for undifferentiated recurrence; MDR for relapse; and HIV for reinfection. The results could guide TB programs in targeting follow up beyond treatment completion for patients at risk, in order to timely detect and treat recurrent TB. Heterogeneity between studies ranged from moderate to high.

### OA-40-746-24 Systematic review and meta-analysis of the association between recurrent tuberculosis and HIV infection

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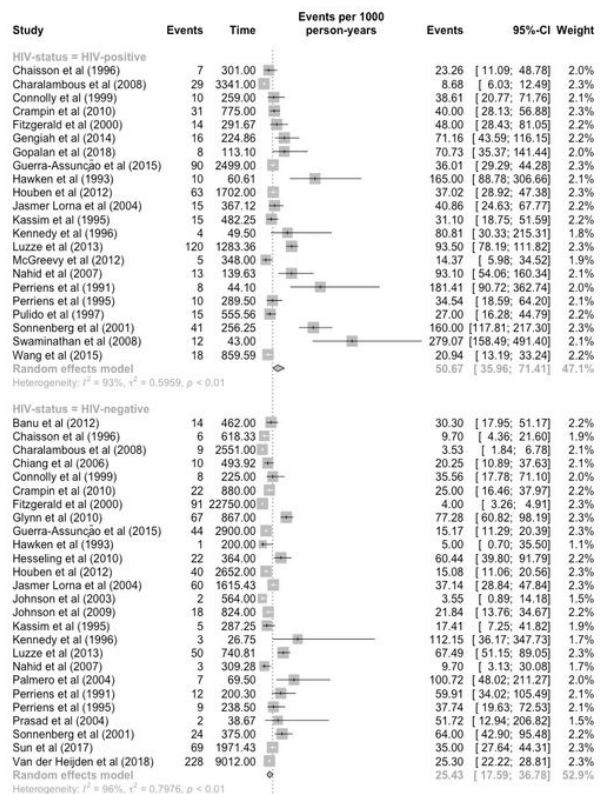
**Background:** TB patients living with HIV may be at higher risk of adverse long-term TB outcomes such as recurrent TB than HIV negative ones. We aimed to review the frequency of recurrent TB and the risk of developing recurrent TB, exogenous reinfection and relapse according to HIV status.

**Design/Methods:** We searched three databases for cohort and case control studies and clinical trials published from January 1980 until October 2019 in three languages. We selected studies that assessed TB recurrences in HIV-positive and HIV-negative patients and calculated recurrent TB incidence rates.

For the subset of studies permitting so, we analyzed the risk of developing recurrent TB, reinfection and relapse according HIV status. We extracted or calculated rela-

tive risk estimates and 95% confidence intervals (CI). Random effects model meta-analysis of rates and risk estimates was performed with RStudio Version 1.1.463. We tested for heterogeneity with the I<sup>2</sup> statistic.

**Results:** The pooled recurrent TB incidence rate was 50.7 per 1000 person-years follow up (95% CI 35.9-71.4, I<sup>2</sup>=93%) among HIV-positive individuals in 22 studies and 25.4 per 1000 person-years (95% CI 17.6-36.8, I<sup>2</sup>=96%) among HIV-negative ones in 26 studies. Heterogeneity was high. (Figure 1) In 16 studies assessing HIV as a risk factor for recurrence, we calculated a pooled RR of 2.47 (95% CI 1.79-3.40, I<sup>2</sup>=75%). Heterogeneity was moderate. In studies (n=11) that discriminated relapses from reinfections, the pooled RR of HIV positivity was 4.64 (95% 2.00-10.74, I<sup>2</sup>=51%) for reinfection and 0.87 (0.6-1.28 I<sup>2</sup>=31%) for relapse. Heterogeneity was moderate.



[Figure 1. Forrest plot of the recurrent TB rate in HIV+ and HIV- patients]

**Conclusions:** The frequency of recurrent TB is more than double among HIV-positive patients compared to HIV-negative ones. HIV positivity does not seem to be a significant risk factor for relapse but it is a strong one for reinfection. The role played by immunosuppression and unceasing exposure to health care services in reinfection should be explored and, when possible, mitigated.

## OA-41 TB detection and treatment in mothers and children

### OA-41-747-24 Increasing Active TB Case Detection Rate among Children in Nine Sub-Saharan Countries: The CaP-TB Intervention

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**Background:** Challenges in diagnosing pediatric TB result in severe under-detection of active TB. A comprehensive case-finding intervention could help improve pediatric TB case detection. This is the first evaluation of a multi-country, multi-pronged intervention to improve pediatric TB case detection.

**Design/Methods:** 130 health facilities were purposively sampled across nine sub-Saharan countries (Cameroon, Côte d'Ivoire, DRC, Kenya, Lesotho, Malawi, Tanzania, Uganda, and Zimbabwe). Sites received training on screening and diagnosis of pediatric TB, mentorship for pediatric-specific symptom screening in waiting areas (including lay workers) of various entry points, increased access to Xpert MTB/RIF testing through strengthened sample collection and transport, and intensified household contact investigation (HCI) for child contacts (0-14 years) of TB index cases.

Using a pre-post intervention design, pre-intervention data (12 months) were retrospectively collected from facility registers starting six months before data extraction. Intervention data of varying periods per site (mean= 8.9 months from start of intervention) were collected prospectively in the same facilities using a project form.

Averages, proportions, and monthly rates were calculated using descriptive statistics. Pre- and post-intervention comparisons of monthly rates and proportions of bacteriological confirmation were done using T-Test for two dependent means and Z-score for two independent populations, respectively.

**Results:** The site-averaged monthly rate of pediatric TB diagnosis significantly improved by 39% in the intervention period (2.31) as compared to the pre-intervention period (1.66) ( $p=0.0009$ ).

Additionally, 11% (14/130) of facilities were newly capacitated for pediatric TB diagnosis through the intervention. The proportion of bacteriologically-confirmed cases significantly improved by 45% from 12.8% (295/2,309) pre-intervention to 18.6% (466/2,508) during intervention ( $p<0.0001$ ).

	Pre-intervention (n=116)*	Intervention (n=116)*	% of Improvement	p Value
Average months evaluated/site	12.0	8.9	N/A	N/A
Cases diagnosed with active TB	2,309	2,508	N/A	N/A
Average monthly TB case detection rate/site	1.66	2.31	+39%	$p=0.0009$
% bacteriological confirmation among TB cases	12.8%	18.6%	+45%	$p<0.0001$

\* 14 of the 130 sites sampled were newly capacitated in pediatric TB diagnosis through CaP-TB intervention and were therefore excluded from the pre-/post- intervention comparison.

[Table 1: Pediatric TB diagnosis comparison, pre- and post-intervention]

**Conclusions:** Implementation of pediatric-focused case-finding approaches like systematic TB screening in waiting areas of various health services and HCI, combined with improved access to Xpert MTB/RIF, significantly improved case detection and bacteriological confirmation of pediatric TB and should, therefore, be prioritized for further scale-up and use.

### OA-41-748-24 Facility-based active case finding for tuberculosis among children: experience from the public and private sector of Bangladesh

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**Background and challenges to implementation:** Non-specific symptoms of tuberculosis (TB) in children make the diagnosis difficult, resulting in missed patients. Each year around 1 million children fall ill with TB. Out of estimated 35,000 child TB patients, only 11,334 (32%) patients were notified in Bangladesh in 2018. Active case finding (ACF) can minimize this gap and increase the detection of TB in children.

**Intervention or response:** From the outpatient departments (OPDs) of three public and 37 private health facilities in Mymensingh district, all children were verbally screened from November 2018 to December 2019. Mobile application with a decision support system was used by trained health workers at the facilities to screen children for symptoms of TB. Children with possible TB were referred to physicians for clinical and laboratory evaluation (Smear microscopy, GeneXpert, Chest X-ray, Histopathology, etc.). Children identified with TB were put on treatment following the national guidelines.

**Results/Impact:** A total of 216,936 children were screened, and 6,361 (3%) children with possible TB were identified and clinically evaluated by physicians. Among the possible child TB patients, laboratory tests were advised for 5,264 (83%) children, and 501 (10%) chil-

dren identified with active TB. Among all identified, 490 (98%) started treatment. The private sector yielded 37% of total child patients. The mean age for children diagnosed with TB was ten years, and 258 (51%) of them were female. Pulmonary and extra-pulmonary TB detected were 329 (66%) and 167 (34%), respectively. The number needed to screen was 433, and the number needed to test was 10. A 96% increase in child TB detection from the baseline in Mymensingh district was achieved through ACF.

**Conclusions:** Facility-based ACF intervention in both public and private settings can act as an effective mechanism for increased child TB detection to minimize the notification gap in Bangladesh.

### OA-41-749-24 Role of urban DOTS approach on tuberculosis case finding among infertile women in Kabul: a document review

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**Background and challenges to implementation:** In 2019, totally 52,770 all form of TB cases detected. 57% (29873) of all cases of TB were among women. Of all TB cases, 13,720 (26%) were extra pulmonary (EP) TB, makes 37 cases per 100,000. Considering diagnostic limitation of EP TB, the actual EPTB could be higher than reported. The USAID-funded STAR project supported NTP to sustain urban DOTS approach in 26 private hospitals in Kabul including Shefajo private hospital. This hospital attended infertile women and tested them for TB. We evaluated the yield of TB among infertile women.

**Intervention or response:** We signed a memorandum of understanding with obstetrics & gynecology (Ob/Gyn) Shefajo hospital and conducting a baseline assessment. The NTP trained medical staff on: TB SOPs, improved supervision, monitoring, and feedback; and conducting active screening to identify presumptive TB patients. The staffs collected cervix swab and tested by GeneXpert or PCR technology. The NTP technical team reviewed data collected from 2017-2019 using standard NTP reporting tools.

**Results/Impact:** From 2017-2019, approximately, 2,400 Ob/Gyn patients attended this hospital and of them, 270 (11.2%) were infertile that tested for genital TB. The mean age was 25 years with average infertility duration of 5 years. Finally, 190 (70%) of them were diagnosed as TB. All were put on standard NTP treatment regimen. The hospital followed all for monthly check up and follows up tests. Among all on TB treatment, 91 (48%) became pregnant at the end of TB treatment. The yield of TB was 7600 in 100,000 among infertile women that is 40 times higher than estimates of 189 in 100,000 for general population.

**Conclusions:** Urban DOTS services in Ob/Gyn private hospital in Kabul made significant improvements in case finding among women and recommend engaging other Ob/Gyn private hospital in TB service provision. Further, the yield of genital TB among women particularly infertile is higher than TB among general population.

### OA-41-750-24 Systematic Review of Symptom-Based Screening and Added Value of Chest Radiography in Screening Pediatric Contacts for Tuberculosis in High-Incidence Countries

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**Background:** The WHO recommends tuberculosis (TB) preventive therapy in child contacts of confirmed index cases after exclusion of active TB. Symptom-based screening remains the most feasible approach to exclude TB, however its capacity to rule out TB compared to chest radiography in different age bands has been questioned.

We performed a systematic review to assess the performance of symptom-based screening as compared to chest radiography in household child contacts below 15 years in the WHO high-burden countries.

**Design/Methods:** Screening of manuscripts published prior February 2019, followed by data extraction was performed by two independent reviewers. Primary outcomes are the concordance between symptom-based screening and chest radiography using the prevalence adjusted bias adjusted kappa coefficient (PABAK) and the proportion of asymptomatic children with negative chest radiography. Secondary outcomes include negative predictive value (NPV) and sensitivity of symptom-based screening against chest radiography read by two independent experts and the proportion of asymptomatic children who developed TB during follow-up. Subgroup analysis in children below or above 5 years was performed.



**Results:** Of 577 identified articles, 30 were assessed for full text eligibility and six met criteria for inclusion. Overall, PABAK varied between 0.16 (95 % confidence interval (CI) 0,04–0,28) and 0.69 (0,59–0,79) and the percentage of asymptomatic children with a negative chest radiography ranged between 54.5–100% (Table).

Study, year	Country	Age group	Sample size	SS- with CXR-/SS-*	PABAK (95% CI)	Agreement	Sensitivity (95% CI)	NPV (95% CI)
Birungi et. al. 2015-2016	Rwanda	0-4	94	100,0%	0,51 (0,33 – 0,69)	moderate	100,0%	100,0%
		5-14	122	100,0%	0,84 (0,74 – 0,93)	almost perfect	100,0%	100,0%
Malik et. al. 2014-2016	Pakistan	0-4	529	97,5%	0,35 (0,27 – 0,43)	fair	one radiography reviewer	
		5-14	377	87,5%	0,89 (0,84 – 0,93)	almost perfect		
Bonnet et. al. 2012-2014	Uganda	0-4	279	97,4%	0,22 (0,10 – 0,33)	fair	81,8% (59,72%–94,81%)	97,4% (93,9%–98,9%)
Triasih et. al. 2010-2012	Indonesia	0-4	119	70,8%	0,09 (-0,08 – 0,27)	slight	40,0% (23,87%–57,9%)	70,8% (63,8%–76,9%)
		5-14	141	84,6%	0,22 (0,06 – 0,38)	fair	39,1% (19,7%–61,5%)	84,6% (79,4%–88,7%)
Fortunato et. al. 2007-2009	Angola	0-4	124	54,5%	0,23 (0,05 – 0,40)	fair	one radiography reviewer	
Kruk et. al. 2004	South Africa	0-4	252	95,5%	0,59 (0,49 – 0,69)	moderate	one radiography reviewer	

[Table. \*SS- with CXR-/SS- = proportion with negative symptom screening (SS) and negative chest radiograph (CXR) out of all children with negative symptom screening.]

In three studies with follow-up data, only 0.4–1.2% of asymptomatic children developed TB.

**Conclusions:** Despite low concordance between symptom-based screening and chest radiography, most studies showed that symptom-based screening alone is effective in classifying children unlikely to have tuberculosis, suggesting that they don't need chest radiography. Lack of standardization in chest radiography reporting and use of different definitions could explain low performance in some studies.

## OA-41-751-24 A systematic review of Xpert MTB/RIF and Xpert Ultra diagnostic accuracy for detection of active pulmonary tuberculosis and rifampicin resistance in children

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**Background:** Xpert MTB/RIF and Xpert Ultra are World Health Organization (WHO)-recommended molecular tests that detect tuberculosis in children with signs and symptoms of tuberculosis. We performed a systematic review on the diagnostic accuracy of these tests in children (< 15 years) with presumed pulmonary tuberculosis for an updated WHO policy on molecular assays intended as initial tests for diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance.

**Design/Methods:** Searched multiple databases to 29 April 2019 without language restriction for studies that evaluated Xpert MTB/RIF and Xpert Ultra in sputum, gastric aspirate, stool, or nasopharyngeal specimens. For tuberculosis detection, reference standards were culture and a composite reference standard. Two review authors independently extracted data and assessed study quality using QUADAS-2. We used the bivariate model to estimate pooled sensitivity and specificity with 95% confidence intervals (CIs).

**Results:** We included 49 studies, which provided 299 data sets (68,544 participants) for pulmonary tuberculosis. Xpert MTB/RIF pooled sensitivity (defined by culture) was 64.6% (55.3 to 72.9) for sputum, 45.7% (27.6 to 65.1) for nasopharyngeal aspiration, 73.0% (52.9 to 86.7) for gastric aspiration specimens, 61.5% (44.1 to 76.4) for stool specimens. Pooled specificity ranged between 98.1% and 100%. Xpert Ultra pooled sensitivity (defined by culture) was 72.8% (64.7 to 79.6) for sputum and 45.7% (28.9 to 63.3) for nasopharyngeal aspirates. Pooled specificity was > 97.5% for both specimen types. Risk of bias was low for all domains, except unclear for the reference standard, because many studies collected only one specimen for culture.

**Conclusions:** We found Xpert MTB/RIF sensitivity to vary by specimen type, with gastric aspirate specimens having the highest sensitivity, followed by sputum and stool, and nasopharyngeal specimens the lowest; specificity in all specimens was > 98%. Compared with Xpert MTB/RIF, Xpert Ultra had higher sensitivity and slightly lower specificity for sputum and nasopharyngeal specimens.

## OA-41-752-24 Population pharmacokinetics and potential new optimized fixed-dose combinations of rifampicin, isoniazid, and pyrazinamide in paediatric patients with tuberculosis

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**Background:** The WHO revised doses for first-line anti-tuberculosis drugs in children in 2010. We estimate drug exposures under these dosing guidelines, explored possibilities for dose optimization using the available fixed-dose combinations (FDC's), and suggest new FDC's with revised weight-bands to achieve optimal dosing of rifampicin, isoniazid and pyrazinamide.

**Design/Methods:** Children 0.2-12 years old receiving first-line drugs for drug-susceptible TB, were studied prospectively in Malawi and South Africa. Intensive sampling at steady-state was performed. Data was analysed using nonlinear mixed-effects models to simulate  $AUC_{0-24}$  with existing FDC's using WHO-recommended doses, and with an optimized tablet number to achieve rifampicin exposures like those reported in adults. Finally, new FDC's and revised weight-bands were designed to achieve literature-based target  $AUC_{0-24}$  ranges of 38.7-72.9 (rifampicin), 11.6-26.3 (isoniazid) and 233-429 mg·h/L (pyrazinamide).

**Results:** Plasma concentrations were measured in 849 samples from 179 children (42% female; 9% HIV-infected; median [range] age 1.9 [0.22-12] years; weight 10.7 [3.20-28.8] kg). Bioavailability of stringent regulatory authority-approved rifampicin was assumed. Using recommended doses of 1, 2, 3 or 4 tablets of FDC (rifampicin/isoniazid/pyrazinamide 75/50/150 mg) for weight bands 4-7.9, 8-11.9, 12-15.9, and 16-25 kg, respectively, simulated rifampicin  $AUC_{0-24}$  amongst children >3-months old was up to 50% lower than reported in adults. Increasing the number of tablets resulted in adequate rifampicin exposures, but high isoniazid and

pyrazinamide exposures. A new FDC (rifampicin/isoniazid/pyrazinamide 120/35/130 mg) with 1, 2, 3, or 4 tablets in weight bands <6, 6-13, 13-20 and 20-25 kg and 0.5 tablet in <3-month-olds with immature metabolic pathways, would improve exposures to all three drugs (Figure 1).

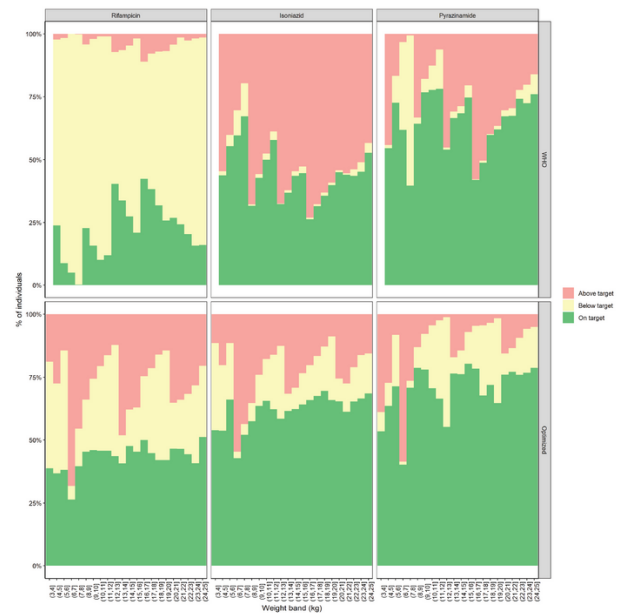


Figure 1. Percentage of individuals within (green), below (yellow) and above (red) the target range for rifampicin (left), isoniazid (centre) and pyrazinamide (right) on WHO-recommended dose and FDC (top row) and with new FDC and revised weight-bands (bottom row).

[Figure 1. Percentage of individuals within (green), below (yellow) and above (red) the target range for rifampicin (left), isoniazid (centre) and pyrazinamide (right) on WHO-recommended dose and FDC (top row) and with new FDC and revised weight-bands (bottom row).]

**Conclusions:** Using current doses and FDC, rifampicin exposures in children were lower than in adults. Optimal doses across all drugs and weight bands cannot be achieved with current FDCs. We propose a new FDC formulation to be used in revised weight bands.

## OA-41-753-24 Pregnancy and birth outcomes in multidrug-resistant tuberculosis patients treated with regimens including new and repurposed drugs

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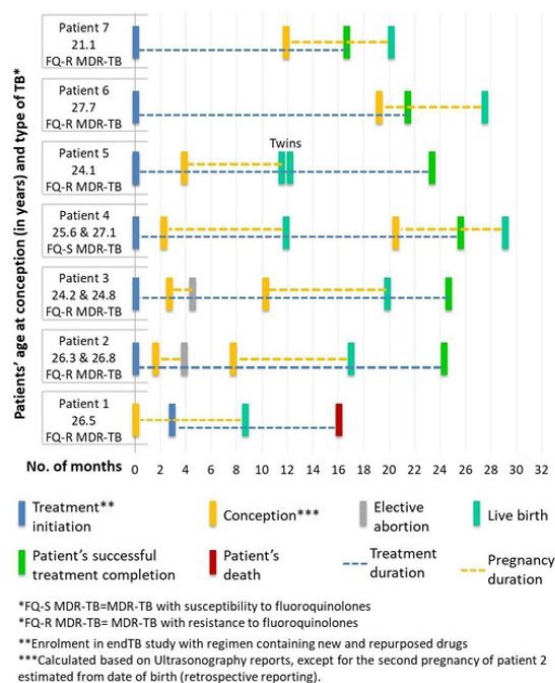
**Background:** In Pakistan, among the 369,548 notified multidrug-resistant tuberculosis (MDR-TB) cases in 2018, 42% were adult females, predominantly in the reproductive age group. There is limited evidence on teratogenic effects of MDR-TB drugs in humans, including newer and repurposed drugs: Bedaquiline, Delamanid, Linezolid and Clofazimine. Hence, patients are advised to use contraception, and offered termination of pregnancy if they conceive prior to or during treatment.

**Design/Methods:** We collected data on conception, birth (up to neonatal period) and treatment outcomes for pregnant MDR-TB patients enrolled on individualized treatment as a part of the endTB Observational Study. In this study, efficacy and safety data was collected on patients initiated on routine MDR-TB treatment between May 2016 and September 2018 at three treatment sites across Pakistan.

**Results:** Out of 145 females of child-bearing age (15 - 49 years) included in the cohort, 9 (6.2%) reported 12 incidences of pregnancy; of these, 3 (33.3%) reported a second pregnancy during the same treatment. 3 (25%) of the 12 pregnancies resulted in elective abortion. Of the 9 remaining pregnancies, 1 (11.1%) is ongoing and 8 (88.9%) pregnancies among 7 patients (See Figure 1) resulted in the live birth of 9 babies (gestation period range: 32.86 – 40.71 weeks) with no reported congenital anomalies.

Among these 8 pregnancies, patients were receiving the following new and repurposed drugs when they conceived: 7 (87.5%) Bedaquiline, 2 (25%) Delamanid, 7 (87.5%) Linezolid, and 3 (37.5%) Clofazimine.

**Conclusions:** In the absence of clear evidence to support increased risk of treating pregnant women with new and repurposed MDR-TB drugs, the benefits outweigh risks to mother and fetus. In our experience with pregnant women, some infected with highly drug-resistant forms of tuberculosis, favorable treatment and birth outcomes were observed. Programs should collect routine data so more evidence is available on best practices to inform local and global policy.



[Figure 1. Conception, pregnancy outcome, and treatment outcome timelines of 7 patients]

## E-POSTER SESSION (EP)

### EP29 The European TB experience

#### EP29-376-24 Exploring the differences between groups of tuberculosis cases with unknown treatment outcomes in Germany

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**Background:** Surveillance of tuberculosis (TB) treatment outcome is essential for monitoring success and gaps of TB control efforts, in particular for understanding the reasons why cases are lost to follow-up, potentially resulting in unfinished treatment.

**Design/Methods:** Using national TB surveillance data for Germany, we analysed TB cases notified between 2013-2018 with unknown treatment outcomes. We compared cases reported as having missing treatment outcome ("missing") to those with unknown treatment outcome due to transfer out of the jurisdiction of the responsible public health office ("transfer out"). Using descriptive and logistic regression analyses, we compared age, sex, resistance profiles, and most frequent countries of birth between the two groups. Due to the delayed reporting of treatment outcomes, descriptive and logistic regression analyses for resistant and multidrug-resistant TB (MDR-TB) were restricted to 2013-2016.

**Results:** Our results show that the groups with reported "transfer out" and "missing" treatment outcomes differ significantly. "Transfer out" cases were on average:

- (i) slightly younger (Odds Ratio (OR)=0.98, 95% CI: 0.98, 0.99);
- (ii) had higher odds of being male (OR=1.62; 95% CI: 1.35, 1.94);
- (iii) higher odds of having resistances to any anti-TB medication (OR=1.38; 95% CI: 1.13, 1.67); and,
- (iv) higher odds of having MDR-TB (OR=1.63; 95% CI: 1.08, 2.45) in comparison to cases with "missing" outcomes.

"Transfer-out" cases were more frequently born abroad and much less frequently born in Germany (Table 1).

**Conclusions:** In Germany, TB cases notified with "transfer out" compared to "missing" treatment outcomes present significant differences in characteristics based on the variables collected within the national TB surveillance system. However, socioeconomic variables such as employment status or homelessness, which could further explain missing treatment outcomes, are not available. Further efforts should be undertaken to improve data completeness and understand reasons for existing absent treatment outcomes in German national TB surveillance system.

Characteristic	"Transfer out" cases		"Missing" cases		Total population†	p-value‡
Mean Age (years)	38 (n=1138)		44 (n=5742)		48 (n=31563)	<0.001
Male Sex	80% (n=908)		68% (n=3879)		66% (n=20915)	<0.001
Drug resistant TB*	30% (n=230)		19% (n=383)		25% (n=5241)	<0.001
MDR-TB**	7.8% (n=41)		2.4% (n=36)		2.1% (n=425)	<0.001
Top 5 countries of birth***	Country	% (n)	Country	% (n)	Country	% (n)
	Romania	13.6% (155)	Germany	23% (1345)	Germany	29% (7916)
	Somalia	7.5% (85)	Eritrea	8.6% (492)	Somalia	6.9% (1758)
	India	6.0% (68)	Somalia	8.1% (466)	Eritrea	6.5% (1520)
	Afghanistan	4.3% (49)	Romania	4.9% (282)	Romania	4.2% (1057)
	Eritrea	3.9% (44)	Syria	3.7% (113)	Afghanistan	3.8% (988)

† The column "Total population" presents the characteristics of the overall population of TB cases notified in Germany.

‡ P-value is given for the comparison of "Transfer out" and "Missing" treatment groups.

\* Reported resistance to any of the following anti-TB medications: isoniazid, pyrazinamide, ethambutol, rifampicin, streptomycin, moxifloxacin, ofloxacin, amikacin, kanamycin, capreomycin, cycloserine, linezolid, p-aminosalicylic acid, prothionamide, rifabutin, levofloxacin. Cases included in the analysis were notified between 2013-2016, with information on their treatment outcomes extracted on March 1, 2019.

\*\* Multidrug resistant TB; cases included in the analysis were notified between 2013-2016, with information on their treatment outcomes extracted on March 1, 2019.

\*\*\* The top 5 countries of birth were selected separately for "transfer out" and "missing" categories, as well as for the total population of included TB cases, based on frequency of occurrence of the countries of birth in each particular category.

[Table 1. Summary of descriptive analysis comparing TB patients with reported "transfer out" and "missing" treatment outcomes]

#### EP29-377-24 Can future tuberculosis cases be predicted in the Netherlands? What you see, is what you get!

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**Background:** In two decades, the number of TB patients in the Netherlands declined from 1,443 in 2000 to 759 in 2019 (incidence 9.1 and 4.4 per 100,000 population respectively). We studied trends to predict future cases.

**Design/Methods:** We used surveillance data from the National TB Register to classify TB patients into five sub-groups:

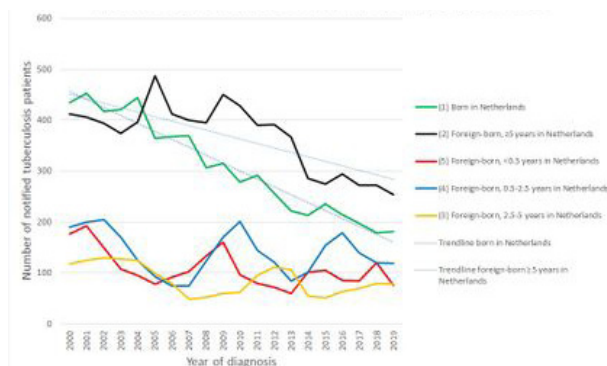
- (1) born in the Netherlands,
- (2) foreign-born ≥5 years,
- (3) foreign-born 2.5-5 years,
- (4) foreign-born 0.5-2.5 years, and
- (5) foreign-born <0.5 years in the Netherlands.

For foreign-born patients who entered the Netherlands between 2000-2015, we calculated ratios for every cohort year of entry by dividing the numbers of patients diagnosed 0.5-5 years by <0.5 years in the Netherlands ( $[(3+4)/5]$ ).

**Results:** The number of TB patients born in the Netherlands declined linearly by 5.2% per year (95% CI: 4.7-5.8) and the number of foreign-born TB patients ≥5 years in the Netherlands by 2.6% per year (95% CI: 1.6-3.6). The number of foreign-born TB patients <0.5 years in the Netherlands ('prevalent cases') fluctuated between 2000 and 2019 and correlated with the inflow of migrants. The trends of foreign-born TB patients diagnosed 0.5-2.5 and 2.5-5 years post-entry followed the same pattern as the one of prevalent cases, e.g. peaks



in the prevalent sub-group were followed by peaks in these two sub-groups in consecutive years (figure 1). The ratio between foreign-born cases 0.5-5 years and <0.5 years in the Netherlands varied between 1.43 (cohort 2004) and 2.81 (cohort 2014); the average ratio was 1.95.



[Figure 1. Tuberculosis patients in the Netherlands by sub-group, 2000 - 2019]

**Conclusions:** Whereas the incidence of TB declined steadily among native and foreign-born patients  $\geq 5$  years in the Netherlands, the incidence among foreign-born patients  $< 5$  years in the Netherlands fluctuated. The number of TB patients diagnosed within 0.5 years after arrival predicted quite accurately the number of cases occurring within 0.5-5 years post-entry, i.e. about two times the prevalent cases.

## EP29-378-24 Tuberculosis health care seeking among contacts of active TB patients: evaluation of symptom screening in a nationwide contact investigation in the country of Georgia

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**Background:** A nationwide TB contact investigation program in the country of Georgia evaluates contacts for TB symptoms providing referrals for TB diagnostic procedures; however, linkage to TB care is not monitored. This study aimed to estimate the proportion of contacts with TB symptoms and determine whether contacts with TB symptoms (cough, fever, night sweats, weight loss, chest pain) were more likely to seek TB care.

**Design/Methods:** We conducted a cohort study among household and close contacts of patients with pulmonary TB diagnosed during 2015-2016. Epidemiologists administered questionnaires to contacts who were then cross-linked with National TB Surveillance databases to identify those who were

- 1) tested for TB and,
- 2) diagnosed with TB (through 2019) by GeneXpert, AFB smear, or culture.

**Results:** 5512 contacts of 1478 active TB cases were enrolled; median age of contacts was 27 (IQR=33) years and 56.1% were female. At least one TB symptom was reported by 209 (3.8%) contacts. Among those contacts with symptoms, 71 (34.0%) received a diagnostic test for active TB, compared to 8.0% (423 out of 5303) of those without symptoms (age and sex adjusted OR 5.7; 95% CI 4.2, 7.8). Among 494 contacts tested for TB, median time from contact investigation to diagnostic test was 28 days; 287 (58.1%) were diagnosed with active TB disease. The TB incidence rate was 1052 (95% CI 924-1194) per 100,000 person-years. Incidence was significantly higher

in contacts with  $\geq 1$  symptom (5904/100,000) compared to those contacts without symptoms (888/100,000; rate ratio 6.7, 95% CI 4.8-9.3).

**Conclusions:** Contacts with  $\geq 1$  symptom were more likely to seek care for TB, and more likely to have active TB compared to contacts without symptoms. Most contacts with symptoms were not identified in surveillance databases, suggesting they did not seek medical care. Additional measures are needed to ensure that symptomatic contacts are linked to care.

### EP29-379-24 Molecular characterization of *Mycobacterium tuberculosis* isolates in the Russian region with unexpectedly low TB incidence

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**Background:** The Vologda region is located in the North of European Russia and is characterized by unexpectedly low tuberculosis (TB) incidence of 15.8/100,000 in 2018 (Russian average - 44.4). We aimed to assess the molecular population structure of *Mycobacterium tuberculosis* here in order to understand the pathogen-related factors that could explain this relatively favorable intriguing situation.

**Design/Methods:** A total of 82 isolates recovered in 2018 from newly diagnosed TB patients were studied. Drug susceptibility testing was performed using BACTEC MGIT 960. The isolates were assigned to the Beijing genotype and its major subtypes based on analysis of specific markers. The Beijing isolates were typed by 24 MIRU-VNTR loci. Non-Beijing isolates were subjected to spoligotyping.

**Results:** Majority of isolates were assigned to the Beijing genotype (51/82; 62.2%). Thirty-one non-Beijing isolates represented 16 spoligotypes of genetic families: T (13.4%), LAM (8.5%), Haarlem (6.1%), Ural (4.9%); unknown family (3.6%). The following subtypes of the Beijing genotype were identified: B0/W148 (n=6; 7.3% of all collection), Central-Asian/Russian (34; 41.5%) and Central Asia Outbreak (CAO)-cluster (7; 8.5%). Thirty-five isolates (42.7%) were drug susceptible, 33 (40.2%) were MDR. The MDR group was dominated by Beijing genotype (25/33). All 6 B0/W148 and 7 CAO isolates were resistant to  $>2$  drugs. In contrast, 11/21

isolates of Central Asian/Russian clade were susceptible. MIRU-VNTR-typing of 51 Beijing isolates revealed 23 profiles (HGDI=0.854); the largest clusters were 94-32 (n=18) and 95-32 (n=8).

**Conclusions:** *M. tuberculosis* population in Vologda (as elsewhere in Russia) is dominated by the Beijing genotype but the prevalence rate of the Russian epidemic clone B0/W148 is 1.5-2-fold lower than in the neighboring provinces. On the other hand, circulation of the resistant Central Asia Outbreak strain is higher than in other Russian regions and warrants close monitoring and analysis of routes of its importation here.

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### EP29-380-24 Treatment of Rifampin-resistant tuberculosis with an all-oral regimen containing new drugs in Zhytomyr Ukraine

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**Background:** Ukraine is a country with high-burden Rifampin-resistant and multidrug-resistant forms of tuberculosis (RR/MDR-TB) (10,000 new cases per year) and poor treatment success rates (49.4%). In August 2018, the World Health Organization has recommended all-oral shorter regimens that contain bedaquiline, linezolid and fluoroquinolones to be developed and used under operational research conditions. We assess the effectiveness, safety, and tolerability of an all-oral 9-12 month regimen containing new drugs for the treatment of RR/MDR-TB in Zhytomyr, Ukraine.

**Design/Methods:** This is an interim analysis of an uncontrolled, longitudinal quasi-experimental study that is planned to enroll 300 RR/MDR-TB patients from 2019 to 2022. We report 6 months culture conversion and occurrence of severe adverse event (SAE) among patients enrolled from March to July 2019 and completed six months of therapy.

**Results:** Among 74 patients included, median age (IQR) was 41 years (34-53), 20 (27%) were female, 14 (20%) were HIV-positive, 30 (47%) had alcohol use disorder (AUD) and 35 (47%) were previously treated for TB. Fifty-three (72%) patients initiated on regimens with bedaquiline and levofloxacin, and 21 (28%) patients initiated on bedaquiline and delamanid. Among 54 with a positive baseline culture, 54 (100%) converted after 2.0 (IQR: 1.0-2.9) months. Fourteen out of 74 patients (19%) had at least 1 SAE, of which one led to treatment

change within six months and eight to death. Up to May 2020, 18 (24%) patients cured, 36 (49%) completed, 2 (3%) failed, 2 (3%) LTFU, 9 (12%) died, and 7 (9%) are still on treatment.

**Conclusions:** Excellent early effectiveness and encouraging safety were demonstrated by this pragmatic study from a high RR/MDR-TB burden setting. Our data contribute to the growing evidence-base on new all-oral regimens, while we continue to collect data on feasibility, comorbidities such as AUD and patient-centered outcomes including quality of life.

### EP29-381-24 Implementation and acceptance of video consultation in the treatment and care of drug sensitive tuberculosis and (Latent) tuberculosis infection in The Netherlands

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**Background and challenges to implementation:** In accordance with the national tuberculosis guidelines, nurses specialized in tuberculosis management counsel patients with tuberculosis and (L)TBI during their treatment. E-Health, in the form of video consultation, has the potential to support counselling. This study focused on the acceptance of video consultation by patients and nurses and aims to provide guidance for nurses considering video consultation.

**Intervention or response:** We used the application We-SeeDo, that complies with National data protection legislation and is ease to use. Nurses from eight Municipal Health Centres (GGD's) in the Regional Expertise Centre North East assisted patients for three to six months through personal and telephone contact, supplemented by video consultation. Half of the patients were counseled through personal contact and by phone only, the other half additionally got video consultation. Outcome measures were acceptance by participants and effect on the supervision pattern.

Patient acceptance was evaluated by the consent to participate in the study, reasons for exclusion and satisfaction after the supervision. Acceptance by the nurses was evaluated by the satisfaction of every contact reported in logbooks and by an evaluation interview.

The effect on the supervision pattern was investigated through logbooks, type of contact, its duration and (saved) travel time.

**Results/Impact:** The patient acceptance rate was 63%. TB patients (67%) had a higher acceptance rate than LTBI patients (56%). Participants were overall satisfied and positive. The counseling pattern was very diverse. The pilot period of six month was therefore too short to find overall effect of video consultation on the counselling pattern. Both a reduction in travel time and an increase in number of short contacts were seen.

**Conclusions:** The pilot was successful. The nurses in the study understand the possibilities and technical limitations of video consultations. Experience of the pilot contributes to the implementation of video consultations at other GGD's in The Netherlands.

### EP29-382-24 A European TB Strategy Toolkit: supporting the development and strengthening of national TB programmes in European Union and European Economic Area member states

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**Background and challenges to implementation:** Although TB incidence has declined steadily across the European Union (EU) and European Economic Area (EEA), attributable in part to timely diagnosis and rapid treatment of infectious cases, a steeper rate of decline must be achieved if WHO targets for TB elimination by 2030 in low-incidence countries are to be attained. This implies a need for country-specific evidence-based TB strategies.

**Intervention or response:** Commissioned by the European Commission and supported by ECDC and WHO Europe, this European TB Strategy Toolkit aims to support national TB plan development or improvement by providing up-to-date guidance on core components of a TB Action Plan or TB Strategy by consolidating the latest EU/EEA-focused evidence and expert opinions involving 31 EU/EEA Member States.

The development of the European TB Strategy Toolkit was underpinned by a portfolio of evidence within the context of the EU/EEA, consisting of two systematic reviews on the effectiveness of TB control and prevention interventions, and barriers and facilitators to their implementation as well as using expert consensus. This informed the development of nine core components for a National TB Plan or TB Strategy. Expert consensus was developed using a 3-round modified Delphi approach involving TB stakeholders, which identified priority areas and activities to mitigate specific barriers to implementation.



**Results/Impact:** The following three priority areas: raising awareness of TB in the community and primary care; reaching under-served groups; screening for latent TB infection and active TB in migrants from high-incidence settings were selected by expert consensus as relevant to TB Action Plans and TB Strategies but difficult to implement.

**Conclusions:** This European TB Strategy Toolkit is aimed at all professionals dealing with TB. It is grounded in the European context, supports prioritisation of areas for action and equips Member States with underpinning evidence to develop national strategic TB plans to move countries and Europe toward TB elimination.

### EP29-383-24 The use of totally implantable central venous access ports system for the treatment of multidrug-resistant tuberculosis. Belarus prospective cohort study

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**Background:** Despite new and repurposed TB drugs have radically altered the landscape for treating multidrug-resistant tuberculosis (MDR-TB) by shifting it to all-oral regimens, some MDR-TB patients (with advanced resistance profile or not tolerating medications) still need intravenous infusions of carbapenems. The use of totally implantable central venous access port system (CVP) helps to avoid daily infusions *via* peripheral veins during the treatment period.

**Design/Methods:** In June 2015 Belarus National TB Program with support from Médecins Sans Frontières piloted CVP use for MDR-TB patients. Following a pilot project results CVP use was programmatically expanded with Global Fund support in October 2016. Patients who started treatment with new MDR-TB regimens containing carbapenems were invited to implant CVP. Patients with CVP were prospectively monitored in countrywide cohort.

**Results:** By 1 May 2020, 194 CVP were implanted in 192 patients: median age 37 years (range: 14-68); 74% male; 78% previously treated; 14% co-infected with HIV. The following veins were used as a route: right (46) and left (8) subclavian, right (87) and left (7) jugular; right cephalic (44) right femoral (2). Eleven (6%) complications were observed, 9 of which (5%) required removal, 2(1%) CVP

were re-implanted: pneumothorax -1 (pleural tube -1); lumen occlusion -2 (removal -2 and re-implantation -2), soft tissue infection -5 (removal -5), venous thrombosis -3 (removal -2, anticoagulant therapy -1). All patients and health care providers (HCP) with previous experience of long-term therapy with intravenous (IV) infusions reported advantage of CVP over the other types of IV access.

**Conclusions:** In Belarus countrywide cohort the use CVP for MDR-TB patients on carbapenem containing regimens demonstrates good safety profile and high level of patients and HCP acceptability.

### EP30 Where are the undiagnosed TB cases?

#### EP30-384-24 Active TB case finding targeted at high burden health facilities in Nigeria: Results from a pilot intervention

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**Background and challenges to implementation:** Hospitals in high tuberculosis (TB) burden countries with limited resources can act as TB transmission hotspots. Is systematic screening in hospital outpatient departments (OPDs) a successful strategy to increase TB case finding and treatment?

**Intervention or response:** The active TB screening of hospital attendees was a USAID-funded intervention implemented in four states in Nigeria from May to September 2019 code-named "TB Surge." Trained cough monitors in collaboration with OPD nurses conducted systematic screening using TB symptom checklist. This was combined with continuous capacity building, provision of high-capacity solar panels for GeneXpert power optimization, logistics for sample movement where necessary, and electronic data reporting for real-time performance monitoring. Presumptive TB was further evaluated using GeneXpert MTB/Rif and Chest x-ray as applicable, and confirmed TB cases were linked to Directly Observed Treatment Short-course (DOTS) and notified to National TB Program (NTP). Case finding results after the pilot phase were analyzed.

**Results/Impact:** During the implementation period, 509,818 hospital clinic attendees were screened across 49 high-volume hospitals. Overall, 43,437 presumptive

TB were identified, of whom 4,319 were diagnosed with active TB and initiated treatment. The average monthly TB case finding increased from 523 cases at baseline to 955, representing an 82% increase in TB notification. Two thousand five hundred and forty-nine (53%) of the TB cases were bacteriologically confirmed.

**Conclusions:** Active TB screening of hospital outpatient department attendees significantly increased TB case finding. Based on the lessons learned from this pilot, NTP is now expanding active TB screening approaches, the TB Surge intervention in high volume hospital outpatient departments nationwide.

### EP30-385-24 Improving TB case finding in hospital outpatient departments: lessons from a health system strengthening approach

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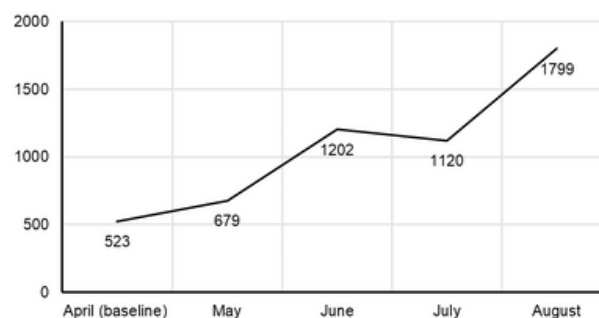
**Background and challenges to implementation:** Nigeria has one of the highest burdens of TB (524 cases per 100,000) and MDR-TB (national prevalence: new 2.9%, retreatment 14.3%) in the world per national prevalence estimates. However, TB treatment coverage remains low (28%). To achieve End-TB strategy, innovative strategies to case finding must be intensified.

**Intervention or response:** Through the USAID-funded Challenge TB project, KNCV supported 49 high-volume health facilities across 4 states in Nigeria to conduct active TB screening at hospital outpatient departments (OPDs) and improve case finding. Capacity building, provision of high-capacity solar panel for GeneXpert power optimization, support for ad-hoc staff, logistics for sample movement, and electronic reporting for real-time performance monitoring were instituted. We reviewed performance data for the intervention period, May to August 2019, across the implementing health facilities, and compared monthly TB yield with baseline.

**Results/Impact:** In the month before this intervention started, the 49 intervention facilities notified 523 TB cases (all forms). During the intervention period, monthly TB notification increased progressively from 679 in May to 1,799 in August, representing an average increase of 129% of TB case notification compared to the baseline (523). Overall, 509,818 hospital attendees were screened, 43,437 (9%) presumptive cases were identified, and 4,319 TB cases were notified.

**Conclusions:** Systematic screening of hospital outpatient department attendees by building the capacity of healthcare workers significantly improved TB case find-

ing. Innovation using real-time electronic data capture and data analysis of key performance indicators played a critical role in optimal performance monitoring.



[Figure. Monthly TB case notification among OPD attendees screened]

### EP30-386-24 Achieving end TB strategy: screening for tuberculosis (TB) in pregnant and non-pregnant women in reproductive age group. Findings from an observational study in Pune, India

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**Background:** TB screening in women is challenging though peak incidence of active TB occurs during reproductive years. We document the prevalence of active/suspected and latent TB (LTBI) and challenges faced in screening reproductive aged women in India.

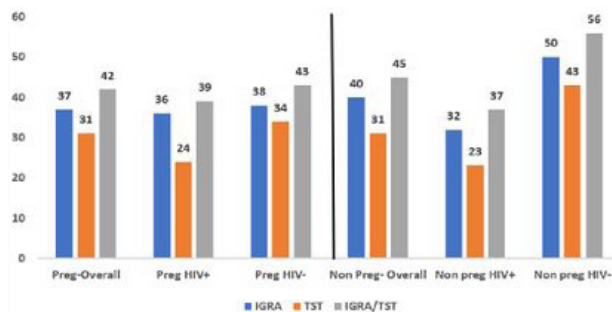
**Design/Methods:** From 2016-2019, we screened consenting pregnant and non-pregnant women for enrolment into an observational cohort study on pregnancy, HIV and TB, in Sassoon Hospital, Pune, India. World Health Organization (WHO) symptom screen, interferon gamma release assay (IGRA) and tuberculin skin test (TST) were used for screening. Positive screening test/s triggered active TB evaluation with sputum gene Xpert, chest X-ray and abdominal ultrasonography.

**Results:** We screened 498 pregnant (115 HIV+) and 644 non-pregnant women (371 HIV+). Prevalence of undiagnosed active/suspected TB was 1.6% (n=8) in preg-

nant and 2.8% (n=18) in non-pregnant women. 62% pregnant and 72% non-pregnant women with active/suspected TB were HIV+.

Over 80% non-pregnant women with active TB tested positive for both screening tests. However, 25% and 63% of pregnant women tested positive for TST and IGRA respectively.

Of the 26 active/suspected TB, 6 pregnant (75%) and 7 non-pregnant women (39%) had pulmonary TB. 50% of pregnant and 22% of non-pregnant TB cases were sputum gene-xpert positive. Of the 13 extrapulmonary TB 62% was abdominal TB by ultrasonography. Prevalence of LTBI (defined as IGRA+ or TST+) was 42% and 45% in pregnant and non-pregnant women, respectively. Challenges listed by study team in screening these women included: need for family to approve participation, reluctance to undergo investigations without any symptoms, time constraints because of competing domestic responsibilities, fear of x-ray in pregnant women.



[Figure. LTBI by tests - pregnant and non-pregnant women]

**Conclusions:** While using an enhanced TB screening approach, a high burden of LTBI and active/suspected TB was observed in both pregnant and non-pregnant women with and without HIV. Challenges need to be addressed to achieve the End TB strategy in this important population.

### EP30-387-24 Active case finding for tuberculosis among factory workers: Punjab, India

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**Background and challenges to implementation:** The WHO and International Labour Organization have highlighted high-risk workplaces as an area of focus for TB prevention and control activities. The Indian Ministry of Health and Ministry of Labour have also tailored policies to safeguard employees. However, an apprehension of losing employment continues to deter factory workers from participating in TB screening.

**Intervention or response:** An active case-finding intervention was established with the consent of factory owners in the districts of Ludhiana and Jalandhar, Punjab covering over 500,000 workers. Since January 2019, active screening was conducted at factories with registrations and referrals facilitated by healthcare workers.

In addition, banners were placed on factory premises with contact details of project staff and factory managers. All workers were informed to call the number to seek assistance for TB symptoms of cough and fever.

The first phase of the intervention consisted of screening and referring presumptive cases for smear microscopy. The second phase of the intervention added a free chest x-ray (CXR) to the screening and referral process.

**Results/Impact:** Within 12 months of implementation, 13,520 factory workers were screened; 1,170 (9%) were presumptive cases, and 157 (15% of evaluated) were diagnosed with TB.

The first phase of the intervention with smear microscopy alone yielded 272 presumptive cases (7%) and 4 diagnosed TB cases (2% of evaluated).

The second phase of the intervention with an added free CXR yielded 898 presumptive cases (9%), and 153 diagnosed TB cases (18% of evaluated). To mitigate fear of losing jobs, the intervention worked closely with factory management to ensure visible support.

**Conclusions:** Active case-finding in high-risk workplace environments can increase awareness and confidence among workers to seek care. Provision of free CXRs substantially increases yields and demonstrates a clear value-add to workers.

### EP30-388-24 Tuberculosis treatment outcomes among patients identified through Active Case Finding in a high-density urban township in Lusaka, Zambia

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**Background and challenges to implementation:** Zambia like many other countries, in line with the World Health Organization, WHO guidance has embarked on Active Case Finding, ACF as a strategy to increase Tuberculosis, TB case detection. However, there is growing concern that clients identified through ACF may have poorer treatment outcomes as a result of lower health-seeking motivation in comparison to a client that seeks health care in a health facility passively.

**Intervention or response:** Treatment outcome data were abstracted from TB treatment cards, clinical records and treatment registers for the 203 TB patients that were identified in a ten-day ACF campaign conducted in June 2018 at Kanyama First Level Hospital and its catchment community in Lusaka Zambia. Individual patient interviews were also conducted to collect supplemental information and as a data verification mechanism. Outcome data was tracked at the end of the treatment period using the treatment register and classified as favourable (cured/completed) or unfavourable (treatment failure/loss to follow up/died/not evaluated).

**Results/Impact:** All the 203 patients identified through the 2018 ten-day ACF were initiated on Anti-Tuberculosis Treatment, ATT. The proportion of favourable outcomes was 94% (n=191), and 6% (n=12) proportion of unfavourable outcomes. The mortality rate was 4% (n=8), lower than the national average of 6%, whilst lost to follow up and not evaluated were both at 1% (n=2) respectively. We observed a high treatment success rate (94%) which is above the national average of 89%.

**Conclusions:** From the findings of this study, we have no reason to believe that TB patients diagnosed through Active case Finding in Zambia have poorer treatment outcomes in comparison to those identified passively provided they are supported throughout the treatment period by routine programme intervention that optimizes treatment support. More research is needed to increase the patient pool before generalizations on ACF performing better than passive case findings can be made.

### EP30-389-24 The yield of school-based active TB case finding in Oromia Region of Ethiopia

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**Background and challenges to implementation:** Ethiopia is one of the high TB burden countries. Estimates indicate that one-third of incident TB cases are not detected each year, which has not improved in the past years despite considerable efforts.

**Intervention or response:** Oromia Regional TB Program started a pilot implementation of TB screening among high school students in West Shoa Zone of the region from October 1, 2019, to April 30, 2019 where case-detection was estimated at <43% in past ten years.

In each of the 11 districts, mass-TB screening was done in one high school, with 16,323 students including 228 teachers. In addition anti-TB clubs were established at school level and a monthly TB day was scheduled to educate students on signs and symptoms of TB. The students held TB education every month on TB day in

their own school. In other hand following monthly TB day, the students were sent to the households to screen TB at the end of each weekend when the students are back to their rural families to restock their weekly supplies including food.

**Results/Impact:** With the six-month implementation period, 122 TB patients (5 teachers and 98 students) identified from the school and 24 additional TB cases were identified from the community by school students. After intervention The case detection rate in the 1st 2nd and 3rd quarter were estimated at 43%, 56%, and 61% respectively.

**Conclusions:** We demonstrated that through school-based TB screening in a high-burden country, additional TB cases can be identified, and there is added advantage of using school students to engage them in community and household presumptive TB referral and the case finding can be scaled up across the country.

### EP30-390-24 Strengthening active tuberculosis case finding: results from using an Active Case Finding toolkit at health facilities in Uganda

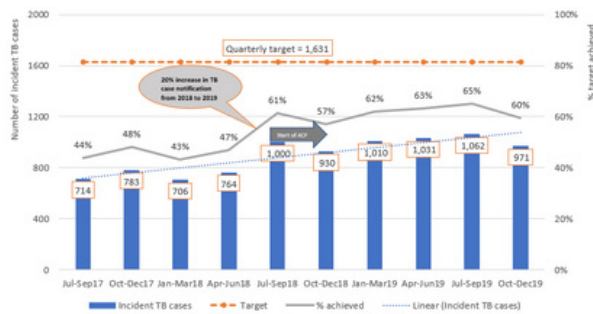
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**Background and challenges to implementation:** Nearly a quarter of the estimated tuberculosis (TB) patients in Uganda were missed in 2018. To address the TB notification gap, the National TB and Leprosy Program (NTLP) using findings from its national TB services assessment in June 2018 developed the Active Case Finding (ACF) toolkit with objectives to improve quality of TB screening, increase case detection and ensure effective treatment at health facilities.

**Intervention or response:** The ACF toolkit was implemented in forty health facilities from nine districts in two regions contributing one-third of the missed TB cases nationally. USAID Defeat TB project supported NTLP to roll out implementation of the toolkit which entails; revitalizing the facility quality improvement teams to coordinate TB services, instituting systematic TB screening at each care point and disseminating ACF tools for use at health facilities. The NTLP trained health workers on how to use the toolkit and conducted quarterly mentorship on GeneXpert use and laboratory logistics management, enhanced clinician's capacity to use X-ray for clinical diagnosis of TB and monitored performance using district health information system.

**Results/Impact:** Quarterly TB notification increased from 44% of expected TB cases in July-September 2017 quarter, to 60% in October-December 2019 quarter.

Overall, TB notification increased by 20% from 3,400 patients in 2018 to 4,074 patients in 2019. Of these, 61% were male and proportion bacteriologically confirmed increased from 44% to 48% in the same period.



[Figure. TB case notification trends in 40 health facilities]

Challenges in implementation of the toolkit included contact tracing of registered TB patients and linkages of private providers to screen and refer patients for TB testing.

**Conclusions:** Implementation of the ACF toolkit led to detection of additional TB patients. Strengthening efficiency of TB screening and expanding GeneXpert testing as initial diagnostic test for TB is recommended for effective implementation and scale up of initiatives to improve TB case finding in countries with substantial missed TB patients.

### EP30-391-24 Active TB case finding among HIV key populations and their contacts – an effective intervention model

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**Background:** The key populations (KPs) for HIV (MSM and FSW) and their close community (KPC) are at increased risk of acquiring TB, and they may not be reachable through routine TB services targeted towards general population (GP).

**Design/Methods:** Population Services International (PSI) Myanmar had provided TB diagnosis and treatment services for people living with HIV (PLHIV) at 12 Targeted Outreach Program (TOP) centers since 2015 and around 100 TB-HIV co-infected cases were detected yearly.

In September 2017, these services were expanded to include TB active case finding (ACF) activities among both KPs and KPC through peer outreach workers. Peer workers conducted health education and symptomatic

screening of TB among KPs and KPC, and referred presumptive TB cases to the nearest TOP and public TB centers for further diagnosis and treatment.

**Results:** From September 2017 to September 2019, peer workers referred a total of 7,903 presumptive TB cases (5131 KPs and 2772 KPC). Among the presumptive referrals, 1,018 (12.9%) were diagnosed with TB and registered for treatment at TOP centers. The percentage of registered TB cases among the presumptive referrals were higher among KPC than KPs (20.4% vs. 8.8%). ACF contributed to 92% of total TB cases registered at TOP centers (1,018/1,106) while the rest (88 cases) were detected among walk-in patients. Nearly 90% of presumptive referrals from ACF activity had never been screened for TB before. Among the 1106 registered TB cases, 778 (70%) were non-PLHIV detected by ACF activity.

**Conclusions:** TB ACF activities among KP for HIV and their close community could detect additional TB cases, which might otherwise be missed by general population TB screening programs. Hence, such TB ACF activity should be continually strengthened and expanded to reach more KPs and KPC undeserved by routine TB services.

### EP30-392-24 Integrating tuberculosis case finding into house-to-house polio vaccination campaigns: findings from the July 2019 supplemental immunization activities in Anambra State, Nigeria

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**Background and challenges to implementation:** In July 2019, the World Health Organization supported the Anambra State Primary Healthcare Development Agency in partnership with the State TB Control Program to integrate TB case finding into the Polio vaccination campaign. Given the significant national pool of 'missed TB cases', the key objective of the intervention was to improve TB case finding from the communities leveraging on the already existing polio structures.

**Intervention or response:** Vaccination teams were trained to simultaneously ask for symptoms of TB whilst vaccinating eligible children in households. Details of presumptive TB cases were documented and community TB volunteers subsequently tracked the reported presumptives for sample collection, shipment, and return of results. Data on presumptives and cases found were reported by the teams. We report the number of cases found, and proportion of wards that reported.



Univariable and multivariable logistic regression analyses were used to estimate the relationship between ward level characteristics and cases reported. The crude and adjusted Odds Ratios with associated 95% confidence intervals are also reported.

**Results/Impact:** Over the four days of the vaccination campaign, 281 presumptive TB cases were reported with 32 being diagnosed as TB cases. Of the 330 wards in the state, 70 (21%) reported at least a presumptive TB case while 18 (5%) of wards reported confirmed TB cases. Wards in peri-urban slums were most likely to identify presumptive TB cases adjusted OR 11.52 (95% CI = 1.62 – 81.79) while wards in Riverine areas were most likely to find a TB case adjusted OR 3.59 (95% CI = 1.16 – 11.01). **Conclusions:** Integrating community TB case finding into already existing structures and activities for house-to-house vaccination campaigns can boost TB case notification and interrupt transmission in communities. Our findings also suggest that this approach is most impactful in peri-urban slums and riverine areas known to be perennially underserved by routine healthcare services.

### EP30-393-24 Intensified case finding among outpatients and their companions by using Chest XRay with artificial intelligence software for tuberculosis triaging in the Philippines

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**Background and challenges to implementation:** 36% of persons with active tuberculosis (TB) in the Philippines remained undetected or unreported in 2018. In the 2016 National TB Prevalence Survey, 43.9% of participants believed their TB symptoms were insignificant, while chest Xray (CXR) was more sensitive than symptom-based screening (92% versus 32%, respectively). Patients' companions are not normally included in TB screening in health facilities.

**Intervention or response:** From August 2019 to March 2020, the USAID's TB Innovations and Health Systems Strengthening project implemented intensified case finding among adult outpatients and their companions in two tertiary public hospitals located in two large cities in the Philippines by using chest XRay (CXR) with artificial intelligence (AI) software for TB triage and Xpert MTB/Rif testing for TB diagnosis as well as profiling TB signs, symptoms and risk factors.

**Results/Impact:** 2,275 people accepted TB screening by CXR. 54.5% were outpatients and 45.5% companions. Although presence of TB signs and symptoms were similar between outpatients and companions (>75%), outpatients were more likely to be male (39.0% versus 34.2%), ≥ 60 years old (20.9% versus 12.7%) and have at least 1 TB risk factor (64.0% versus 55.7%). 27.4% of participants had presumptive TB either by AI-triaged CXR and/or TB signs and symptoms, and 82.4% of presumptive TB submitted one sputum sample within 10 minutes of screening. Yield of bacteriological-confirmed TB in outpatients and their companions were 1.75% and 1.23% respectively (p=0.02). 37.6% of diagnosed cases had no signs or symptoms of TB (P=0.000).

	Patients (n=6687)	Companions (n=5588)
Age in years		
15-34	2,098 (31.4%)	1,874 (33.5%)
35-59	3,194 (47.7%)	3,003 (53.8%)
>60	1,395 (20.9%)	711 (12.7%)
Sex		
Male	2,610 (39.0%)	1,909 (34.2%)
Female	4,077 (61.0%)	3,679 (65.8%)
TB risk factors <sup>1</sup>		
Presence of ≥ 1 risk factor	4,281 (64.0%)	3,112 (55.7%)
No risk	2,406 (36.0%)	2,476 (44.3%)
TB signs and symptoms <sup>2</sup>		
Presence of ≥ 1 signs and symptoms	1,612 (24.1%)	1372 (24.5%)
No signs and symptoms	5,075 (75.9%)	4,216 (75.5%)

<sup>1</sup> TB risk factors include smoking, diabetes mellitus, TB contacts, previous TB treatment, >60 years old, urban/rural poor and health care workers

<sup>2</sup> TB signs and symptoms include cough < 2 weeks, cough ≥ 2 weeks, unexplained fever, unexplained weight loss and night sweat

[Table 1. Characteristics of people screened with CXR]

**Conclusions:** These results show that using AI triaging of CXR for TB led to effective and timely sputum submission. Without CXR, 37.6% of TB cases would have been missed. Companions of outpatients are easy to reach and provide high yield of TB. Hospital-based screening of outpatients and companions by using CXR and AI-read triaging in high TB-burden countries can help find undetected TB.

## EP31 Allied against TB: new and old partners

### EP31-394-24 Tuberculosis case yield of at-risk groups using modified screening algorithm in Nigeria secondary and tertiary healthcare facilities

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**Background and challenges to implementation:** Nigeria has one of the lowest case detection rates among the high TB burden countries. The national TB program has identified hospital outpatients as a key population for active TB screening to improve case finding in recent strategic planning. However, questions remain about TB yield in outpatient departments, including the feasibility of enhancing TB case finding.

**Intervention or response:** Between May – September 2019 we conducted active TB screening for individuals attending hospital clinics namely; general outpatient (GOPD), pediatric outpatient (POPD), anti-retroviral (ART), accident and emergency (A&E), antenatal (ANC), medical outpatient (MOPD), and specialized clinics (including diabetes, optics, ear and throat, national health insurance scheme, ward) in 49 high-volume hospitals. Presumptive TB clients were further evaluated using GeneXpert. We compared TB yield and contribution to TB notification based on the number needed to screen (NNS), and test (NNT).

**Results/Impact:** During the intervention period, 509,818 outpatient attendees were screened. Ten percent of those screened were identified as presumptive TB, and 4,319 were diagnosed with TB. Fifty-nine percent of people with TB were GOPD attendees and 4% were MOPD attendees.

The specialized clinics accounted for 18% of TB cases, while ART, ANC, and POPD clinics contributed 7%, 3%, and 9% respectively. NNS was lowest among GOPD attendees ( $n=81$ ;  $p<0.001$ ). NNT was highest among antenatal clinic attendees ( $n=20$ ;  $p=0.03$ ).

Compared to the historical baseline, the monthly TB case notification increased to 80% during the implementation period.

**Conclusions:** Active TB screening in the various outpatient departments improved TB case finding. However, the yield of TB varies significantly across these outpatient clinics and underscores the need to prioritize efforts for a nation-wide implementation given underlying resource constraints.

## EP31-395-24 Engaging informal health care providers in TB case identification-experiences from project in India

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**Background and challenges to implementation:** In country like India, Informal Health Care Providers (IHCP) provide bulk of the initial medical care for any illness. TB care provided by IHCPs is characterized as non-diagnosis, misdiagnosis, and delayed diagnosis and/or in appropriate treatment. These IHCPs are currently neglected under private provider engagement (PPE) initiatives of the country. TB Alert India (TBAI) implemented Project to engage IHCPs in TB program. Project was supported by Stop TB under TB Reach Wave 6 grant. Project was implemented in 8 Tuberculosis Units (TUs) in Telangana state.

**Intervention or response:** After mapping, selection and enrolling IHCPs, training was given on TB, and project, expectations. Enrolled and trained IHCPs were expected to refer patients visiting them with TB like symptoms (PTS) for testing at National TB Program (NTP) clinic, through project developed Mobile application. One Field coordinator (FC) was put in place for 35 - 40 IHCPs to play a catalytic between PTS, IHCPs and NTP. Private CBNAAT & X-ray facilities were also empanelled (to cater the load of NTP facilities) to complete the NTP approved diagnostic algorithm. IHCPs were incentivised for all PTS diagnosed with TB.

**Results/Impact:** Project mapped 1614 and enrolled 755 IHCPs. IHCPs successfully facilitate testing of 97% of the PTS referred (8939/9245), between Oct 2018 to Dec 2019. Gap between referred and tested has decreased from 25% in Q3-2018 (Jul- Sept 2018) to 2 % in Q4 (Oct -Dec 2019). Turnaround time for testing after referral has decreased from 4.5 days in Q3 2018 to 1.36 in Q4 2019. Mobile application helped in reducing the diagnostic delay and initiation of early treatment. An increase of 1748 new notifications were reported in Q4 - 2019 against a baseline of 838 in Q3 - 2018.

**Conclusions:** Engaging of IHCPs is very important for successful PPE strategy for reducing the diagnostic delays and treatment shopping.



### EP31-396-24 Key acceptability constructs influence pharmacist participation during a diagnostic referral pilot in Ho Chi Minh City, Viet Nam

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**Background:** Friends for International TB Relief (FIT) piloted a private pharmacy engagement scheme which used the SwipeRx pharmacy professional social networking app to facilitate verbal screening of pharmacy customers and referral of eligible people for subsidized CXR screening and free follow-up on Xpert testing across four districts of Ho Chi Minh City, Viet Nam during 2019-Q4.

**Design/Methods:** We developed a standardized questionnaire to assess the perceptions of pharmacists who were engaged and trained as part of FIT's pilot on health care intervention acceptability and pilot implementation. 100 in-person surveys were conducted: 50 among pharmacists who made at least one referral and 50 among pharmacists who were trained, but made no referrals. The responses between these two survey cohorts were then compared using the Mann-Whitney U test.

**Results:** Pharmacists making at least one referral had a significantly better understanding of the pilot's objectives (intervention coherence) and were significantly more likely to agree that the pilot would achieve its objectives (perceived effectiveness). They were also significantly more likely to believe that the additional TB screening was beneficial for their business and that it could serve as a unique selling point over other pharmacies in the area (affective attitude). Finally, they were significantly more confident in their ability to use the SwipeRx app for verbal screening (self-efficacy). No significant differences between the survey cohorts were measured on perceptions associated with ethicality, opportunity cost, burden or other aspects of implementation.

**Conclusions:** These survey findings highlight four key acceptability constructs which must be emphasized during the recruitment and training of pharmacists as this pilot is scaled up to additional locations. Any improvements in the perceptions and beliefs around these key acceptability constructs could translate into higher participation rates and increased detection of TB.

### EP31-397-24 Determinants of TB suspects' referrals by pharmacies and over-the-counter medicine shops operators for laboratory TB diagnosis in Eastern Region, Ghana: a telephone survey

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**Background and challenges to implementation:** The community tuberculosis (TB) care strategy adopted in Ghana in 2007 includes involvement of pharmacies and over-the-counter (OTC) medicine shop operators in TB case detection. One objective is to increase referral of TB suspects for laboratory diagnosis. Uptake of this strategy in the Eastern Region is high on account of a collaboration between the regional TB Control Programme and pharmacies. Training sessions are held with community pharmacies and OTC medicine shop operators. Information on the impact of this partnership on TB referral is largely not available. The study assessed the determinants of TB suspects' referral by pharmacies and OTC medicine shop operators using a telephone survey design, the first of its kind to be conducted in Ghana.

**Intervention or response:** In 2019/2020, we included 850 pharmacies and OTC medicine shop operators with phone contacts in the Eastern region of Ghana in a telephone survey using a structured questionnaire. The primary outcome of interest was operators' self-reported TB referral; we used multivariable logistic regression to investigate determinants.

**Results/Impact:** Of all the participants who completed the interviews, 69% (321/467) reported having ever referred a TB suspect of whom 54% (174/321) have no documentation and 72% (337/467) had received TB specific training. In preliminary analysis, factors associated with TB suspects' referral included receiving TB related training (OR=2.6), performing both front and back desk functions (OR=2.1), operating from OTC shop (OR= 5.1), use of taxi or bus as means of transport to TB lab (OR=3.8) and operators opinion in favour of TB referral (OR=17.9).

**Conclusions:** Pharmacies and OTC shop operators largely support TB referral. Their contributions to case detection, however, remain unquantifiable due to policy implementation gaps, which should be addressed.

**EP31-398-24 TB care in prisons in New Delhi**

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**Background and challenges to implementation:** Demographics of prison settings, including their situational and environmental vulnerabilities, increases the risk of contracting TB among prisoners and with around only 30% inmates being convicts, makes the rest a highly vulnerable risk group for transmission of the infectious disease among the population at large. TB prevalence rates are observed about 84 times higher among inmates as compared to the general population and India has about 1400 prisons inhabiting nearly 37 lakh inmates. Tihar is largest Jail in South Asia, inhabiting a floating population of more than 15000 inmates and around 927 inmates in Rohini Jail. Since 2018, NDTBC has initiated the project to screen all inmates for TB symptoms, to diagnose TB cases and provide treatments required, even after their liberation.

**Intervention or response:** A quantitative study was conducted screening all inmates of Tihar jail using ACF data collection tools and one to one interview with structured questionnaire. Inmates having symptoms suggestive of TB were offered X-ray chest PA view and two sputum specimens were collected to perform smear microscopy, Cartridge based nucleic acid amplification (CBNAAT) test and culture examinations, as per the WHO approved RNTCP diagnostic algorithm.

**Results/Impact:** 18492 prisoners were screened, out of which, 1018 (5.5%) were found symptomatic and tested for TB as presumptive cases, and 132 were diagnosed as confirmed TB cases. Estimated overall prevalence of diagnosed pulmonary TB cases among prison inmates was 714/ 100000. Restructuring of policies among all jail authorities ensuring linkages to health care services and provision of regular follow up activities even after the release of the prisoners into the society was strategized.

**Conclusions:** While inmates are at increased risk, so too are the communities to which they return. It is imperative to understand the need for an "Exit screening strategy" and long term follow up of these inmates, preventing population spill over.

**EP31-399-24 How community pharmacies can contribute to early detection and treatment of TB patients in Vietnam? A cross-sectional simulated client survey**

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**Background and challenges to implementation:** Private pharmacies play an important role in the timely referral of patients with presumptive TB. We aimed to investigate how pharmacy staff in Vietnam responded to patients reporting symptoms of presumptive-TB and Multi-Drug-Resistant TB (MDR-TB).

**Intervention or response:** A simulated client (SC) survey was used to collect data from 638 randomly selected pharmacies (community pharmacies or drug counters) from Apr-Nov 2019 in four provinces in Northern (Hanoi and Thanh Hoa) and Southern (An Giang and Ca Mau) regions of Vietnam. Trained actors followed two clinical scenarios:

(a) an adult male presenting with typical symptoms of pulmonary TB and

(b) an adult male presenting with possible MDR-TB.

The appropriate management for both cases was to refer the SC to a healthcare provider, without supplying medications. Data about the interaction were documented after each visit. Descriptive statistics and logistic regression models were employed.

**Results/Impact:** Pharmacy staff referred 155/638 (24.3%) SCs to the TB service. However, 93 (14.6%) followed appropriate practice. Appropriate referrals were higher in MDR-TB cases 116/320 (36.3%) than for presumptive TB cases 39/318 (12.3%).

A higher proportion of pharmacy staff asked SCs about their symptoms in MDR-TB scenario 245 (76.6%) than presumptive-TB scenario 195 (61.3%). Other medical/medication history was requested in 31 (9.7%) and 34 (10.6%) of scenarios. Pharmacy staff who collected a medical history were more likely to refer patients to a healthcare provider, both for presumptive-TB (Adj. OR=3.74, 95% CI: 1.45-9.64; P=0.006) and MDR-TB (Adj. OR=1.85, 95% CI: 0.97-3.52; P=0.060) scenarios, compared to those that did not take a medical history.

**Conclusions:** Many pharmacies in Vietnam did not ask patients about medical history. A minority of patients were referred appropriately. The pharmacy staff's behaviour was more likely to be appropriate if they took a

patient history. Professional training of pharmacy staff is recommended to avoid diagnostic and therapeutic delays for patients with presumptive TB.

### EP31-400-24 Police become partners in the fight against tuberculosis: experience from Kiambu County, Kenya

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**Background and challenges to implementation:** According to Audit of the Criminal Justice System 2016/2017, Kenya is estimated to have 17th highest incarceration rate in Africa with 121 for every 100,000 persons of the population being detained and 500,000 persons passing through the police cells each year. The accused persons are at high risk of contracting Tuberculosis (TB) because of the overcrowding and poor ventilation of cells, vans and court holdings. Screening of the accused persons is not a requirement in police documentation. The police officers lack capacity to screen for TB on admission. Kiambu County is among the high TB burden counties in Kenya. With support from The Global Fund, Amref Health Africa in Kenya partnered with Resources Oriented Development Initiatives (RODI) in collaboration with National TB program and National Police Service (NPS) in Kenya to implement a Kenya Innovation Challenge (KIC) to expand TB screening and finding missing people with TB in police stations and linking them to TB diagnosis and treatment services.

**Intervention or response:** From September to November, 16 police stations were mapped, followed by sensitization of National police management and police staff. A total of 180 officers were reached. Of these, 24 were inducted as liaison officers to support continuous sensitization and screening on admission. Monthly incentive of US\$25 was paid. A total of 4 outreaches were conducted targeting police families and surrounding community. Presumptive cases had their sputum collected and transported to Genexpert sites.

**Results/Impact:** A total of 1,019 persons were screened for TB; 111 prison staff, 275 accused, and 633 civilians. Of these, 11% were presumptive (5% police, 73% civilians, and 23% accused). 3 (all accused persons) were diagnosed with TB and started on treatment.

**Conclusions:** National police service should ensure that all accused persons are screened before admission into the police cell. The strategy would enhance early diagnosis and commencement to treatment.

### EP31-401-24 Understanding profile and treatment practices of Informal Health Care Providers (IHCPs) in RIPEND Project implementation area in Telangana (TS) State, India

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**Background:** IHCPs form an important stakeholder in health care setups providing initial medical care. A quantitative study was taken up to understand the profile and treatment practices of these IHCPs.

**Design/Methods:** Descriptive research design was used in the study. A structured questionnaire was administered to all IHCPs willing to be part of the study (555 were interviewed). Study was taken up from March 2019 to Jun 2019. Data were entered in a standard data entry software (EpiData, Odense Denmark) and was analysed using Epi-Data analysis software.

**Results:** Around 39% of IHCPs were less than 40 years followed by 37% in age group between 40-50 years. Less than 1% of IHCPs were women in contrast to 99.5% men. Around 11% of providers did not complete 10th standard. 35% said they did some diploma course like electrical, mechanical, Lab Technician etc... Around 43% of the IHCPs were practicing between 10-20 years. Around 62% said they worked at a qualified provider, while some said that they learned from their relatives (mostly father who was IHCP). Almost equal percent were running their clinic in own (50%) and rented (48%) buildings. Near about 549 IHCPs (of 555) opened their clinic for 3-4 hours in the morning and evening. Around 13% of the IHCPs informed that they take up home visits on patients request. More than 3/4th of the respondents informed that they see around 10-20 patient per day, number goes up to 40 in rainy season. Consultation fee ranged between INR. 50- 75 for 94% IHCPs. Majority of the respondents said they give some medicine if people come to them for cold and fever initially before sending them for any testing.

**Conclusions:** Engaging/sensitizing IHCPs in TB care is very crucial given their profile of education and treatment practices for early case detection and treatment initiation.

### EP31-402-24 Implementing 100% out patient department screening in a resource limited setting: what has worked

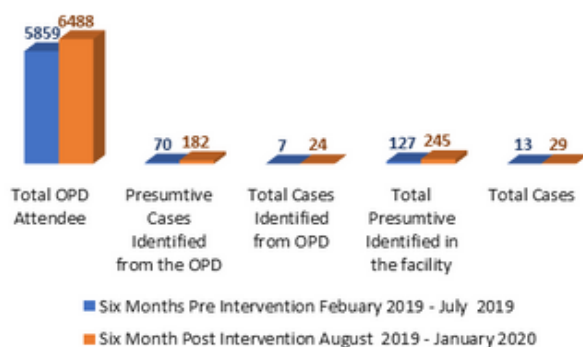
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**Background and challenges to implementation:** The existence of significant missed opportunities for TB clinical screening among symptomatic persons visiting health facilities for non-TB-related services has been demonstrated. This puts healthcare workers and other patients at increased risk of acquiring TB from undiagnosed persons. To this end, faith-based hospitals in Anambra State South-East Nigeria were engaged to conduct TB screening for all hospital attendees.

The aim of this intervention was to implement clinical TB screening using national algorithms on all clients attending out-patient departments of high-volume faith-based hospitals and estimate its impact on the number of TB cases reported by those health facilities.

**Intervention or response:** A Top-bottom implementation model was utilized. Key activities generally followed the same sequence of: advocacy to hospital management, training of health workers on the algorithm and tools, and institution of a facility-OPD screening Team. Each facility team was supported to develop a Presumptive Sample Flow Chart as well as institute quality improvement interventions to cover the existing gaps. Weekly data collection was carried out using nationally available data tools.

**Results/Impact:** Data Collection was done six Months Pre and Post Intervention the result showed that there was a 92% increase in Presumptive Identified in the facilities during the intervention and case finding increased by 100%.



[Figure.]

**Conclusions:** Screening all the OPD attendees for TB using the National Guideline helped increase the total presumptive and TB cases in the facility by 100%. We

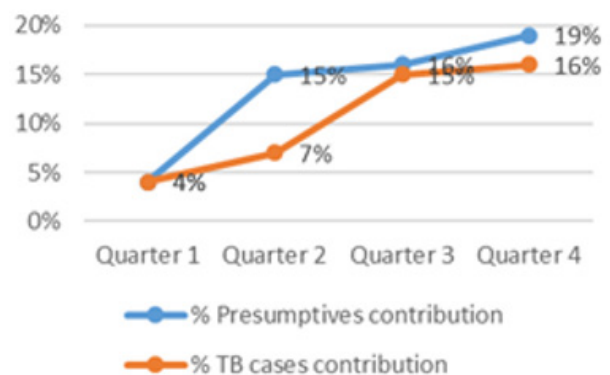
recommend that this model of hospital-based active surveillance is scaled up to all health facilities to reap the maximal benefits.

### EP31-403-24 Periodic performance review with patent medicine vendors; a fulcrum for improving TB case detection in the community: a case study of Nasarawa State, Nigeria

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**Background and challenges to implementation:** Patent Medicine Vendors (PMVs) are the first point of care for a large proportion of patients with chronic cough. Though considered as the informal health sector, PMVs play a key role in Nigeria's health care delivery especially among the rural poor. The objective of the study was to demonstrate the effect of periodic performance review with PMVs in increasing TB case finding.

**Intervention or response:** We identified and trained 120 PMVs across 10 local government areas (LGA) in collaboration with the State TB Program and the National Association Proprietary and Patent Medicine Dealers (NAPPMED). Bi-monthly review meetings coordinated by NAPPMED with technical support from KNCV were held in each LGA to appraise the performance of the PMVs. PMVs were rewarded based on presumptive TB cases successfully referred and TB cases diagnosed. We compared the contribution of PMVs in each quarter to the overall state report from quarter 1 to quarter 4, 2018.



[Figure. PMVs contribution to presumptives and TB cases in Nasarawa state]

**Results/Impact:** RESULT: In Q1 (January–March), PMVs contributed 342 (4%) of the 9540 presumptive TB reported and 25 (4%) of the 625 TB cases notified by the state. In Q2 (April–June), PMVs contribution increased to 637 (15%) of the 4194 presumptive TB reported and

42 (7%) of total 657 TB cases notified. By Q3 (July–September), contributions from PMVs rose to 956 (16%) of 6010 presumptive TB cases reported and 88 (15%) of 606 TB cases notified. By quarter 4 (October–December), PMVs contributed 1155 (19%) of 6157 presumptive TB cases and 107 (16%) of 686 TB cases notified. TB case yield from presumptives identified by PMVs was 9% while the yield from the total presumptives in the state largely from intra-health facility screening was 11%.

**Conclusions:** With Nigeria's low treatment coverage, strategically engaging the informal health sector especially PMVs through NAPPMED presents a unique opportunity for finding and treating missing persons with tuberculosis.

## EP32 Quality improvement of the TB cascade of care

### EP32-404-24 Evaluation of Tuberculosis Active Case Finding (ACF) cascade: results from a TB surge intervention in Akwa Ibom State, Nigeria

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**Background and challenges to implementation:** Following the WHO's End TB strategy, there is a need to focus control efforts on interventions that will effectively contribute to the decline in the burden of TB in Nigeria. Nigeria is among the 30 high burden countries for TB, HIV-associated TB, and multidrug-resistant TB. Low case detection (28%) is largely attributed to passive case finding practices. This analysis aims to showcase the gains of providing multiple diagnostic options for testing.

**Intervention or response:** The TB surge intervention was conducted in 12 KNCV supported sites in Akwa Ibom State. Forty-one ad hoc staff were engaged to support TB screening, documentation, and referral at various service delivery points across all the intervention facilities. Intervention screening registers and modified screening algorithms were used. Mobile diagnostic unit, free pediatric x-ray with logistic support to x-ray sites and Lateral flow urine lipoarabinomannan assay were used to widen the diagnostic options and strict follow-up for testing was closely enforced.

**Results/Impact:** During the intervention period; 39,767 (35.4% male, 64.5% female) clients were screened (75.3% of total hospital attendees). Seven thousand and forty-three (18.4%) presumptive were identified. Six thousand seven hundred and fifty-four (92%) of identi-

fied presumptive had diagnostic evaluation, 873 (12.9%) TB cases were diagnosed. Alternative diagnostic options accounted for testing of 25.1% of all presumptive and 38.9% of diagnosed TB cases. TB case notification increased from 616 to 873 between the baseline months of October 2018 – March 2019 and end line month of May – September 2019.

**Conclusions:** Findings uncovered testing gaps. Ensuring availability and utilization of multiple diagnostic options will close testing gaps thereby leading to improve case detection. There is a need for the National TB program to standardize screening of hospital attendees and ensure continued capacity building for staff on TB ACF as most field workers do not prioritize TB screening to maximize case finding opportunities.

### EP32-405-24 Pay for performance to optimize the tuberculosis care cascade and improve quality of services at high volume health facilities in Kenya

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**Background and challenges to implementation:** The 2016 Kenya Tuberculosis (TB) Prevalence Survey revealed that 80% of people with TB had sought care but were not diagnosed. Inventory studies show 20% of bacteriologically confirmed TB patients in Kenya are either not treated or notified. System challenges e.g. staff shortage and non-conducive work environment cause inefficiencies contributing to attrition along the TB care-cascade.

**Intervention or response:** Amref and National TB Program are implementing Pay for Performance (P4P), a Global Fund supported strategic initiative (July 2019 – June 2021). P4P aims to improve TB case notification and quality of TB services through engagement of facility leadership, comprehensive focus on TB care cascade and motivation of healthcare workers. Facilities earn US\$40 for each additional TB case notified quarterly compared to same quarter, previous year. Additional money is earned for quarterly treatment success rate (TSR) ≥85% to encourage timely updating of outcomes. Data verification is through the web-based TB surveillance system, TIBU. To ensure quality, amounts are adjusted downwards against percentage score on agreed quality indicators. Facilities channel 60% of earnings to improvement of TB services and 40% to motivation of healthcare workers.

From July–October 2019, performance agreements were signed with 13 high-burden counties. County and sub-county health management teams and leadership and staff from 197 high-volume facilities were sensitized and

facility workplans developed. Step-by-step guidelines were provided to facilities to address challenges in calculating amounts due.

**Results/Impact:** In December 2019, two counties submitted claims for July-September 2019. Of 40 facilities that claimed, 31 qualified for payment with 27 having cumulatively increased case finding by 237 despite a decline in the country while 13 had TSR of  $\geq 85\%$ . Collectively, facilities in Nairobi and Homabay earned US\$11,780 and US\$7,280 respectively. Facilities reported increased motivation to offer quality TB services.

**Conclusions:** Incentivization through P4P can motivate health facilities to provide quality TB services and improve TB case notification.

### EP32-406-24 Cascade analysis for Active TB Case finding intervention in Nigeria: a tool for quality improvement and program monitoring

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**Background and challenges to implementation:** To close the gap between estimated and notified Tuberculosis (TB) cases in Nigeria, the National TB Programme and implementing partners have adopted active TB screening. Thus, there is need for systematic analysis of the screening cascade data to identify points of losses.

**Intervention or response:** KNCV Nigeria through funding from USAID is implementing active TB screening in 61 high volume facilities across 9 states. All clinic attendees are screened for TB using a symptom checklist. We constructed a cascade to assess clients' retention across the screening stages 1-6 which are:

- (1) Total Clinic attendees
- (2) Number Screened
- (3) Identified presumptive TB
- (4) Presumptive TB investigated
- (5) TB cases diagnosed
- (6) TB cases on treatment.

We set targets for each stage and designed a template for weekly data monitoring and cascade analysis to measure gaps. We did root cause analysis (RCA) and designed specific interventions to address identified gaps.

**Results/Impact:** Presenting data for early phase of implementation along the 6 cascade steps, 114,944 clients attended clinic (1); of these, 108,047 were screened for TB (2); 12,502 presumptive TB were identified (3); 8,240 of them were tested (4); 766 TB cases were diagnosed (5) and 590 put on treatment (6). There was a 6%, 29% and 22% gap in the number screened, tested, and enrolled

on treatment respectively. RCA done for these identified gaps showed some presumptive TB cases could not produce sputum. Tracking and linking these clients to Chest Xray narrowed the testing gap to 8%. Line-listing and tracking all patients yet to commence treatment showed 53% were on treatment in other facilities while additional 42% were linked to treatment which narrowed the enrollment gap to 5%.

**Conclusions:** Cascade data analysis enabled us to visualize 'what and where' the program performance gaps were, informed a deep dive analysis and course corrections for efficient use of resources. It proved an invaluable tool for program performance monitoring and quality improvement.

### EP32-407-24 Impact of TB cascade Loss in a Facility-based intensified TB case finding intervention in Nasarawa State, Nigeria

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**Background and challenges to implementation:** Recent Global TB reports Nigeria suffers the highest burden of Tuberculosis in Africa. Many undiagnosed cases visit health facilities to access care daily. Previous studies show that high rates of drop off along the TB cascade can lead to underreported TB cases. This study aims to describe cascade loss leading to program gaps.

**Intervention or response:** Between February & March 2020, we initiated an intensified active TB screening at seven selected high burden health facilities in Nasarawa State using ad-hoc staff. They were trained on presumptive TB identification, documentation using the Comcare app and the national presumptive TB register. They screened clients and relatives visiting the health facilities using simplified symptom checklist and presumptive TB cases referred for further diagnostic evaluation using GeneXpert. Their data was analyzed.

**Results/Impact:** Out of a total of 12,672 patients screened in 7 health facilities, 3,687 (29 %) were presumptive TB cases referred to the TB DOTS for immediate evaluation. In the facility presumptive TB register, only 36.1% (1,333) of these referrals made it to the DOTS for further evaluation as 63.9% (2,354) dropped off along the cascade between presumptive identification and diagnostic evaluation.

Of the 1,333 presumptive TB evaluated, 71 (5.32%) cases of TB were diagnosed and commenced on treatment. One rifampicin resistant TB case was detected and referred.

**Conclusions:** The highest rate of drop off along the TB cascade was noted from the point of presumptive identification to diagnostic evaluation and this presents a



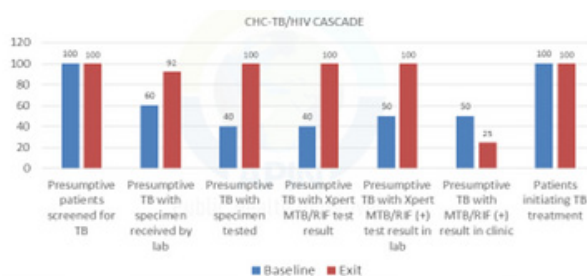
serious challenge to the implementation of intensified TB case finding intervention. . To prevent this, we have placed cough officers responsible for patient escort to the point of diagnostic evaluation who are trained on the safe collection of sputum samples on the spot. We are hopeful this intervention bridges this gap.

### EP32-408-24 Implementation and Scale up of Tuberculosis Clinic-Laboratory Continuous Quality Improvement (TB CLICQI) in Nigeria: Lessons learnt

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**Background and challenges to implementation:** TB case-finding and diagnosis continues to be a challenge overall most especially among People Living with HIV. Nigeria is the 3rd country contributing to 80% of TB missing cases globally. Despite the wide availability of TB diagnosis and treatment, several TB cases are missed within the diagnostic cascade because of poor quality service.

**Intervention or response:** A novel project initiated by CDC was piloted and implemented at 5 health facilities in Nigeria by APIN. TB CLICQI pilot fuelled interest in expanding it in PEPFAR program. All CDC PEPFAR implementing partners were trained by APIN to step down the training to their supported health facilities and apply same interventions that worked. We selected more sites to scale up TB CLICQI at supported health facilities. The organizational program data was used to select ten facilities based on TB-HIV burden. A collaborative implementation Continuous Quality Improvement approach was used to strengthen the weak points along TB-HIV diagnostic cascade.



[Figure 1. Result-3]

**Results/Impact:** Quality Improvement projects were implemented at the selected health facilities. The result of observation and views of Stakeholders' on health system weaknesses that affect quality in TB screening range from non-adherence to guideline/SOPs, lack of knowledge of TB-HIV algorithm and diagnosis, poor documentation to lack of patient privacy. After providing the interventions, quality of documentation improved from

50% to 100%, Presumptive TB data from 68% to 99%, Genexpert TB testing increased from 89% to 100%, TB screening increased from 75% to 100%, Treatment initiation improved from 75% to 100%.

**Conclusions:** Finding the missing cases plays a big role in preventing and reducing TB transmission. CQI activities if instituted at TB and TB-HIV facilities in addition to existing EQA and supportive supervision will curb TB missing cases that occur along the cascade. There is need for commitment by stakeholders to provide sustainable resources for TB/HIV prevention and implementation of CQI.

### EP32-409-24 Finding additional TB cases through symptom screening for diagnosis in high burden setting: cough of 2-weeks is not enough

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**Background and challenges to implementation:** Despite recent progress, improving case finding remains one of the leading concerns of the national TB program in Nigeria. More evidence on strategies to improve case finding is needed to reach End-TB targets.

We report the effort on health-facility based innovative TB screening strategy and determine its impact on case detection.

**Intervention or response:** Between May – September 2019 KNCV, with support from the USAID Challenge TB project, implemented facility-based active TB case finding activities including symptom screening, sputum collection and transport to laboratories, provision of a high-capacity solar panel for GeneXpert power optimization, human resource support, and continuous capacity building for healthcare workers across 49 high-volume health facilities.

The TB symptom screening questionnaire was revised to remove the two-weeks cut-off for cough symptoms for presumptive TB identification. Identified presumptive TB were evaluated using GeneXpert MTB/RIF assay.

**Results/Impact:** During the intervention period, 509,818 clients were screened for TB by cough monitors using a multi-symptom questionnaire. Nine percent of those screened were identified as presumptive cases. Of the 33,836 presumptive cases who completed evaluation for TB, 13% were diagnosed with TB. Eighty-four percent of people with TB had a cough of any duration other constitutional symptoms with or without other constitutional symptoms. Only 11% had a cough of two or more weeks without other symptoms, and 5% had no cough.



Compared with the historical baseline, there was an increase of 80% in monthly TB case notification during the intervention period.

**Conclusions:** The active TB case finding intervention using a multi-symptom TB screening questionnaire followed by GeneXpert MTB/RIF for diagnosis improved case detection significantly.

The findings from this pilot bring up a poser on the two weeks cut-off for presumptive TB identification in the NTP standard TB symptom screening checklist.

This strategy has the potential to shorten diagnostic delay, successfully bring patients into care, and reduce TB transmission.

### EP32-410-24 Prevalence of Mycobacterium tuberculosis in sputum among adult clinic attendees compared with the surrounding community in rural South Africa: implications for finding the missing millions

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**Background and challenges to implementation:** We determined the prevalence of sputum Mycobacterium tuberculosis (Mtb) culture-positivity among adults at two primary healthcare (PHC) facilities in a demographic surveillance area (DSA) in rural South Africa. Concurrently, we conducted a community-based TB survey in the DSA. We compared the prevalence of sputum Mtb liquid culture-positivity in PHCs versus community.

**Intervention or response:** PHCs: Cross-sectional survey of randomly-selected adults ( $\geq 18$  years) attending for their own health were screened for TB symptoms (cough, weight loss, night sweats, fever) and all requested to give sputum for mycobacterial culture. HIV status was defined based on self-report and record review.

**Community:** All adult DSA residents ( $\geq 15$  years) were invited to attend a mobile clinic for general health screening; those reporting  $\geq 1$  TB symptom or whose chest radiograph showed any lung-field abnormality were asked to give sputum for mycobacterial culture. All participants underwent HIV testing.

All participants unable to produce sputum were classified as culture negative.

**Results/Impact:** PHCs: Among 2,055 participants (1,580 [76.9%] female, median age 36 years), 1,460 (71.0%) were classified HIV-positive (76.2% on antiretroviral therapy [ART]), 131 (6.4%) reported  $\geq 1$  TB symptom, and 509 (24.8%) reported current/previous TB treatment.

**Community:** Among 10,320 participants (7,049 [68.3%] female, median age 38 years), 3,005 (29.1%) tested HIV-positive (90.3% on ART), 1,091 (10.6%) reported  $\geq 1$  TB symptom, and 2,414 (23.4%) reported current/previous TB treatment.

Among PHCs 20/2,055 (1.0% [95% CI 0.6–1.5%]) participants were sputum Mtb culture-positive compared to 58/10,320 (0.6% [95% CI 0.4–0.7%]) in the community-based survey.

The table compares characteristics of participants with positive sputum cultures by study:

	Clinic (n = 20)	Community (n = 58)
Age, median (IQR)	37 (32 - 46)	48 (30 - 64)
Male, n (%)	9 (45.0)	28 (48.0)
On TB treatment at enrolment	2 (10.0)	4 (6.9)
Previously treated for TB	5 (25.0)	6 (10.3)
HIV positive, n (%)	15 (75.0)	26 (44.8)
On ART, n (%)	15 (75.0)	21 (36.2)
$\geq 1$ TB symptom, n (%)	6 (30.0)	13 (22.4)
Rifampicin mono-resistant TB, n (%)	1 (5.0)	2 (3.4)
Multi-drug resistant TB, n (%)	4 (25.0)	9 (15.5)

[Table.]

**Conclusions:** The prevalence of Mtb sputum culture-positivity was slightly higher in clinic attendees than the community; in both settings most were asymptomatic. Efforts to interrupt TB transmission may need to extend to communities as well as health facilities, and not rely solely on symptom screening.

### EP32-411-24 A country-tailored package approach to TB case-finding – Challenge TB (CTB) project experience across 23 countries

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**Background and challenges to implementation:** Low TB treatment coverage was a common problem in the 23 countries at the start of the USAID/Challenge TB project; the range of missing TB patients was 50–60% of the estimate along the cascade of care. To accelerate TB case finding, CTB implemented several complementary strategies and interventions which are country-tailored.

The interventions are provided as a package to saturate a specific geographical area. The geographical coverage and duration of implementation varied depending on country priorities.

**Intervention or response:** These interventions include community-based TB case finding, intensified TB case finding in health care facilities (TB screening at OPD and all other service delivery points including ART and pediatric clinics), contact investigation, TB case-finding among key populations, and private sector engagement. **Objectives:** To describe the yield of the different TB case finding interventions to TB case finding.

**Methodology:** Descriptive retrospective analysis of the contribution of different case finding interventions to TB treatment coverage for a period of five years (2015-2019) including results of the package approach.

**Results/Impact:** TB treatment coverage increased from 51% to 67% across all CTB supported countries between 2015-2019. Despite variation by country, across the project, the observed yield was as follows, listed highest to lowest: intensified TB case finding in health care facilities community-based TB case finding, private sector engagement, TB case finding among key populations, and contact investigation. However, countries implementing a package of multiple interventions in one geographical area had a better trend in the TB treatment coverage; examples were Afghanistan, DR Congo, Indonesia, and Tanzania. Limitations of attribution of different interventions to case notification are acknowledged as interventions are complex and not mutually exclusive.

**Conclusions:** Strengthen health care facility TB screening and diagnosis while complementing with a complete and comprehensive package of TB case finding defined based on patient health-seeking behavior and the patient path-way.

### EP32-412-24 Enhancing the performance of newly established TB services sites through the incorporation of structured demand creation activities in Nigeria. Findings from a non-randomized intervention study

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**Background and challenges to implementation:** Worldwide, TB is one of the top 10 causes of death and the leading cause of a single infectious agent with millions of people continuing to fall sick with TB each year. Seeing that diagnosis and successful treatment of people with TB averts millions of death, it is imperative to seek more efficient strategies for improving TB case findings. Thus, the purpose of this study was to determine the impact of structured demand creation activities included as part of TB service expansion activities on improving the identification of presumptive and confirmed TB cases in Northern Nigeria.

**Intervention or response:** A longitudinal prospective study of 100 selected health facilities (50 control and 50 had the intervention) selected for the expansion of TB

services in Kano and Bauchi states, Nigeria. Focal persons in all health facilities were trained with the same materials and manuals on tuberculosis prevention, treatment & control. Health facilities in the intervention group were empowered to conduct advocacies and community outreach in the communities within their environs. Data was tracked and collected using national data tools over a 6-month period. We compared the means of presumptive and confirmed TB cases from both arms of the intervention and report T-test results with associated p-values.

**Results/Impact:** At the end of the 3rd & 6th month of follow up, facilities in the intervention arm recorded a 5% & 11% increase in yield of TB cases from identified presumptive respectively, as against the 1% from the pre-intervention period of the same group. The intervention showed significant yield as highlighted in the table.

	Pre Intervention						Post Intervention							
	N	Presumptives	t	p	Confirmed	t	p	N	Presumptives	t	p	Confirmed	t	p
Control	50	71	-	-	8	-	-	50	865	-	-	38	-	-
Intervention	50	191	2.848	0.005	2	-1.552	0.124*	50	1457	2.674	0.009*	99	3.05	0.003*

Note. Student's t-test.

\*Levene's test is significant ( $p < .05$ ), suggesting a violation of the equal variance assumption

[Table.]

**Conclusions:** It may not be enough to simply improve the capacity of healthcare providers to offer TB services, it is highly recommended that demand creation activities are structured into the TB service expansion programs. Our study demonstrates that this approach will greatly improve TB case finding.

### EP32-413-24 Towards achieving "UNGA political declaration on HIV and AIDS" commitment on TB case finding among PLHIV, in India

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**Background and challenges to implementation:** Tuberculosis is the leading cause of morbidity and mortality among people living with HIV. The UNGA political declaration on HIV and AIDS adopted in June 2016 committed to working towards 100% coverage of intensified TB case finding (ICF) among all PLHIV by 2020. This is reflected in the India's National Health Policy 2017 and the National Strategic Plan for TB Elimination 2017-25 aims to achieve the milestone by 2019. India rolled out single window delivery of TB and HIV services to strengthen ICF across all ART centers from December 2016. This also included screening of all PLHIV during each and every visit to the ART center by various levels of healthcare workers including care coordinator (a peer educator from affected community), staff nurse and medical officers.

**Intervention or response:** We measure the TB screening among PLHIV to assess the coverage of intensified TB case finding. The article presents an analysis of secondary data collected through routine reporting under the National AIDS Control programme from January 2017 to June 2018 and observations made during the field visits to the ART centres.

**Results/Impact:** The number of PLHIV being screened for TB among those attending the ART center increased from 80% in January 2017 to 89% in June 2018, even with an increase in those attending the ART center from 0.86 million to 0.95 million during the same time period. The improvement was a result of intensive monitoring through sharing feedback on performance of the indicator through letters to ART centers, data quality checks, regular review meetings across all levels and capacity building through online sessions and field visits.



[Figure.]

**Conclusions:** India is on track to achieve its annual target of 90% coverage of TB screening of PLHIV as well as UNGA targets. The significant improvement underlines importance of focused review and regular feedback mechanism.

## EP33 Barriers in the TB care cascade: it's time for local solutions

### EP33-414-24 Barriers to care-seeking for tuberculosis in the Philippines: a qualitative study through the lens of behavioral science

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**Background:** Tuberculosis (TB) remains a leading cause of death worldwide and in the Philippines, in part because symptomatic individuals delay or avoid care-seeking. Through the USAID-funded Breakthrough RESEARCH project, this study investigated behavioral barriers to care-seeking among individuals experiencing symptoms suggestive of TB in the Philippines.

**Design/Methods:** This study investigated barriers to care-seeking in a high-prevalence peri-urban area of Pampanga. Through qualitative research and the lens of behavioral science, 116 interviews were conducted with people affected by TB, health providers, community members, and employers exploring perceptions and reactions to symptoms, care-seeking, stigma, and lived and observed experiences of people affected by TB. Data were analyzed using thematic analysis to identify behavioral barriers to care-seeking.

**Results:** Five intertwined behavioral barriers to care-seeking were found to be affected by:

- 1) ambiguous symptoms;
- 2) association of TB risk with lifestyle and habits;
- 3) potential for stigma, discrimination, and isolation;
- 4) anticipated financial burden and threat to identity; and
- 5) visibility of care in public sector facilities.

Findings suggest that for individuals experiencing symptoms, it is a combination of barriers that inhibit care-seeking. Symptomatic individuals face a series of implicit trade-offs related to health, social, and financial consequences of having TB or another serious illness, and of seeking care or not seeking care.

**Conclusions:** The findings suggest that programs to encourage timely care-seeking can more effectively reach those experiencing TB symptoms and their family members to encourage care-seeking by:

- 1) reshaping perceptions of when care-seeking is appropriate,
- 2) disassociating TB, vices and social status,
- 3) reducing enacted, perceived, and self-stigma,
- 4) supporting TB symptomatic individuals to maintain a positive self-identity, and,
- 5) providing discreet ways to access care.

### EP33-415-24 Does exposure to TB meetings, either small or large group, improve the knowledge and health seeking behavior for early TB diagnosis? Experience from Bengaluru and Hyderabad

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**Background:** Health seeking by the right person, at the right time from the right place is crucial for early diagnosis of TB. Tuberculosis Health Action Learning Initiative (THALI) funded by USAID, placed trained local community health workers (CHWs) who conducted small and large group communication activities to improve knowledge and health seeking behaviors.

**Design/Methods:** The project covered 3 Million urban slum population in Hyderabad and Bengaluru cities. We adopted 'baseline' and 'end line' cross-sectional surveys to assess the changes in the knowledge and health seeking behaviors among TB symptomatic adults, in the years 2017 and 2019. Outcome indicators assessed were comprehensive knowledge on TB, sought treatment from a qualified doctor after two weeks of cough and subject's request for sputum tests. We defined program exposure as participation in TB meetings, small or large group. We assessed the effect of program exposure on the outcome indicators, using the nearest neighborhood matching method.

**Results:** In pooled data from both cities, comprehensive knowledge about TB increased from 28% to 40%, sought treatment from a health care provider after two weeks of cough from 58% to 67%, and request for sputum test from 4% to 17% from baseline (2017) to end line (2019) survey. Combined data from both rounds of survey, indicated that seeking treatment from a health care provider was higher in Bengaluru than Hyderabad. Program exposure was significantly associated with increase in all three outcomes examined. If all TB symptomatics were exposed the program, the increase in comprehensive knowledge and examined health seeking behaviors would be 13% and 9% respectively, as compared to none being exposed.

**Conclusions:** Community based activities by trained local community health workers improves both comprehensive knowledge and health seeking behaviors for early TB diagnosis. Increasing population coverage enhances the effect of these activities.

### EP33-416-24 Community engagement activities reduce patient delays in TB diagnosis and treatment initiation in Bengaluru and Hyderabad cities, South India

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**Background:** Effect of community engagement on reducing delays in TB diagnosis and treatment have not been documented so far. We examined the effect of community engagement activities on reducing patient delay carried out under USAID funded Tuberculosis Health Action Learning Initiative (THALI) in Bengaluru and Hyderabad.

**Design/Methods:** We adopted 'pre' and 'post' cross-sectional surveys to evaluate changes in various delays related to TB diagnosis and treatment initiation. The subjects were new sputum positive (NSP) adults who were initiated on treatment within 3 months before the surveys, conducted in Hyderabad and Bengaluru in 2017 and 2019. We examined the changes in average delays between the two periods. Exposure to the program included whether the subject had participated in one-one, small or large group communication with project recruited field staff, known as community health workers, on TB. The effect of program exposure on delay was estimated using the nearest neighborhood matching method.

**Results:** In a pooled data analysis, the mean patient, health system, and total delays reduced from 21 to 10 days, 37 to 18 days, and 58 to 28 days, respectively, with higher reductions in Bengaluru than Hyderabad. In the matching methods analysis, a significant reduction in patient and total delays of 4.2 days (95%CI: -6.3 to -2.0) and 5.4 days (95%CI: -9.5 to -1.3) was seen among those exposed to the community engagement activities, as compared to those who were not

**Conclusions:** Community engagement activities conducted by local trained community health workers can significantly reduce patient and total delays in TB diagnosis and treatment initiation.

### EP33-417-24 Provision of peer support by TB survivors to people with TB, through the TB program in India - Successes, challenges and way forward

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**Background and challenges to implementation:** Psychosocial support to the person with TB and his family, in the form of peer support or otherwise, is vital for treatment adherence, as articulated by the people with TB (PWTB), TB survivors and the program.

**Intervention or response:** The USAID funded Call to Action project trained 229 TB survivors as TB champions (TBCs) and engaged them in provision of psychosocial support which included education on treatment adherence, nutrition, support with alleviating stigma in the family, community and workplace, etc to PWTB in the public sector. We did in-depth interviews of 34 TB champions, 65 PWTB and 28 representatives from the program to understand successes and challenges in provision of peer-support.

**Results/Impact:** The TBCs reached out to 12000 PWTB across 6 states of India. TB champions were able to provide psychosocial support and address stigma confidently, especially in tribal areas where support in local language was sparse. Their major challenges were varied levels of support from field staff and being handed down field-staff responsibilities. In areas where STS (Senior treatment supervisor) coordinated well with TBCs, STS felt TBCs supplemented their activities, especially in remote and hard-to-reach areas and also expressed the need for more champions. Some DTOs (District TB officer) expressed interest in receiving feedback about patient care from TBCs and felt the need for more TBCs, particularly in crowded urban settlements. Factors that were crucial to success of support provision was commitment to involve the TBCs by the DTO, trust and support of field level workers, namely STS, Health visitors and Lab technicians. The DTOs, in most cases felt that TBC led peer - support was a vital need for people who are notified by private sector and for people with MDR-TB.

**Conclusions:** Orientation of district level leadership and field staff to possible benefits of peer support is imperative for institutionalised engagement of TBCs.

### EP33-418-24 Addressing stigma in people living with drug-resistant tuberculosis in India: a Photovoice study

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**Background:** Individuals with Multi Drug Resistant (MDR)-TB undergo 1-3 years of treatment and face intense stigma. We utilized a Photovoice intervention to explore lived experiences of MDR-TB stigma and gauge the efficacy of Photovoice, as a tool, in engaging patients to reflect on these experiences.

**Design/Methods:** Embedded within Participatory Action Research (PAR), the intervention was implemented at the Médecins Sans Frontières MDR-TB project in Mumbai, which attends to 140 MDR-TB patients (64% female). A safe space was created for consenting patient participants to take photos reflecting stigmatizing experiences and share stories in collaborative groups. Through participants' provision, dissemination decisions were taken to raise community awareness. The intervention process and outputs were qualitatively analysed using PAR and stigma frameworks.

**Results:** From December 2019 to January, 2020, nine female participants shared 37 non-identifying images and narratives over ten group discussions. The study revealed the life-altering stigma facing people with MDR-TB, from anticipated and enacted to structural. Loss (of self, voice, status, mobility) and abuse (mental, social) were at the forefront, leading to distress that was characterized by feelings of shame, isolation, suffocation and peril. Education, general or disease related, did not appear to correlate with non-stigmatising or compassionate behaviours received from stakeholders. Marriage deepened women's trauma and loss of agency. Coping mechanisms began with TB detection and included peer/family support, self-motivation and building resilience. Photovoice helped participants connect. The process of sharing deeply emotive images and events enabled participants to confront their fears in solidarity, and uplifted interpretations of past events. For dissemination, changes in the deep-set attitudes and environments which fostered stigma were contemplated.

**Conclusions:** Stigma is a critical social outcome of MDR-TB. Photovoice may be a useful tool for engagement, understanding, and relief of MDR-TB stigma. This is a novel provision in India but appropriate to bring patient voices into MDR-TB debates.

### EP33-419-24 Perceptions about tuberculosis and perceived tuberculosis-related stigma and associated factors among the mining community in Eswatini

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**Background and challenges to implementation:** Stigma continues to undermine efforts to end tuberculosis (TB), particularly among at-high risk populations. This article aims to describe the perceptions of the mining community about TB and the factors associated with perceived TB-related stigma among this subpopulation in Eswatini.

**Intervention or response:** A cross-sectional descriptive quantitative study design was employed and data were collected among the mining community from purposively selected households and mining industries across Eswatini. A researcher-administered electronic questionnaire was used through SurveyToGo software. Proportions were computed and multiple logistic regression was performed.

**Results/Impact:** In total, 163 participants were enrolled, a majority of them aged 36-59 years (68.1%, n=111), male (69.3%, n=113) and current mineworkers (38%, n=62). Up to 84.7% (n=138) perceived TB as a very serious disease. About 74.6% felt health care workers (HCW) have a positive attitude towards patients who come for TB and HIV services, most of them being those who had once accessed the services. Up to 27.6% (n=45) participants had high perceived TB-related stigma scores. Participants aged 19-35 years (adjusted odds ratio (AOR)=1.65, 95% CI: 1.01, 5.44, p=0.047), and those who stayed six years or longer in a community had higher odds of having high TB-related stigma, (AOR=6.38, 95% CI: 1.36, 29.8, p=0.02). However, participants from the Manzini region, had relatively lower odds of having high TB-related stigma (AOR=0.20, 95% CI: 0.05, 0.89, p=0.03).

**Conclusion/Recommendation:** The mining community generally perceives TB as a very serious disease. Nearly a third expressed stigmatising thoughts, mainly anticipated external stigma from health care workers and the community at large. Stigma is associated with younger age, certain geographical areas, as well as having stayed longer in an area. Health education messages about TB and/or stigma need to be reframed into non-stigmatising echoes, and be directed more to younger age-groups and to certain specifically selected geographical areas.

### EP33-420-24 Cost related to diagnosis and care endured by MDR-TB patients in a reference hospital in Cameroon. A transversal exploration

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**Background:** The NTP of Cameroon identifies and treats yearly between 150 and 190 RR/MDR TB patients. Patients are treated with a STR type 'Bangladesh' during the 4months intensive phase under hospitalisation (about 70%) or ambulatory. The declared policy of the NTP is to make diagnosis and treatment free of charge. We determine the costs patients experience due to their TB diagnosis and care as well as magnitude and composition of these costs. As data collection has to be interrupted due to the Covid-19 epidemics, the experienced costs cover only to the intensive hospitalization phase.

**Design/Methods:** This was a cross-sectional health facility-based survey, conducted in the main treatment reference center (Hospital Jamot, Yaounde) between January and begin March 2020. TB patients were interviewed by trained nurses using a standardised questionnaire.

**Results:** Among the 27 TB patients who participated (response rate 81.8%), the median age was 42 years; 85.2% were from the capital, Yaounde. The patient was the main income earner in 51.8% of households. Annual individual and household incomes during the TB episode together - before during, and after TB diagnosis - decreased overall by 92%. Using a cut-off of 20% of annual household income, 78% of patients experienced catastrophic costs related to their TB diagnosis and care. Income loss and nutritional supplementation accounted for respectively 65% and 35% of these costs.

**Conclusions:** 21 of 27 RR/MDR TB patients hospitalised in the main reference center in Cameroon experienced catastrophic costs related to TB diagnosis and care already during the intensive phase of their treatment. The declared and applied interventions of the NTP did not prevent patient expenditures accumulate to catastrophic cost dimensions. Financial and social protection to mitigate against these costs are urgently needed, in addition to universal health coverage.



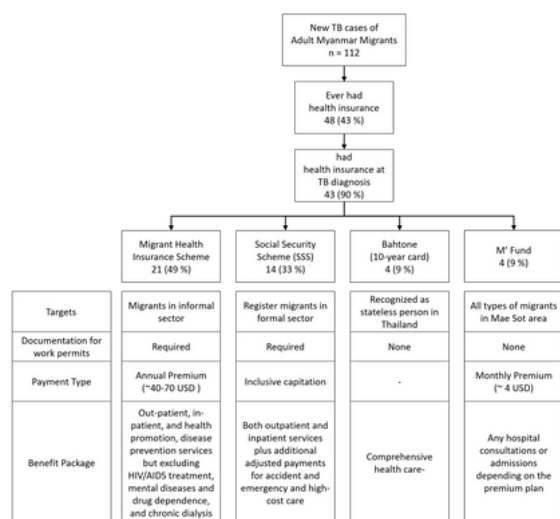
### EP33-421-24 Coverage of health insurance schemes among Myanmar migrants with tuberculosis in a border area of Thailand and its associated factors: an interim analysis

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**Background:** Migrants are a risk group for tuberculosis (TB) with poor access to quality healthcare which is not free. Thailand is one of a few countries in Asia that provides the health insurance (HI) to migrants. This study aimed to assess the coverage of health insurance schemes and its associated factors among Myanmar migrants with TB in a border area in Thailand.

**Design/Methods:** This is a part of on-going cohort study that has been conducted among new TB cases of adult Myanmar migrants within three months of TB treatment in TB clinics of Mae Sot General Hospital and Shoklo Malaria Research Unit since September 2019 in Mae Sot district. The coverage was calculated as percentage and factors associated were analysed using a multivariable logistic regression model. The estimates were presented in adjusted odds ratio (aOR) and 95% confidence interval (CI) with a p value less than 0.05 as significance.

**Results:** An interim analysis including a total of 112 TB migrants showed 48 (43%) were ever insured, of which 90% were still being insured at the time of TB diagnosis. Types of health insurance were Migrant Health Insurance Scheme (21, 49%), Social Security Scheme (14, 33%), and others (8, 18%). Details of insurance are shown in Figure 1.



[Figure 1. Different health insurance schemes and coverage among new TB cases of adult Myanmar migrants in a border area between Thailand and Myanmar]

Migrants who work in factory (aOR=41.4, 95% CI 6.5-262.0), live with family (aOR=13.3, 95% CI=2.5-70.3), and are documented migrants (aOR=3.8, 95% CI=1.2-12.0) were more likely to be insured.

**Conclusions:** Less than half of migrants had health insurance which were the migrants working in factory, living with family, and having documentation. The reasons of having or no having health insurance are important to be explored. Flexible and migrant-sensitive policy through multi-sectoral action plans should be considered to enhance coverage of insurance among vulnerable migrants to combat TB transmission.

### EP33-422-24 Social support for TB patients living in extreme poverty, experience from Bangladesh

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**Background and challenges to implementation:** BRAC, a development organization working on economic empowerment and social development including health. TB has been a priority for BRAC as it was closely related to poverty. BRAC participated in a partnership with the National Tuberculosis Program (NTP) and other non-governmental organizations (NGOs) to increase TB services nationwide. The social support is one of those initiatives that were adopted to overcome the economic, geographical, socio-cultural and health system barriers for TB patients especially those who are living below the poverty line.

**Intervention or response:** To identify and implement social support in End TB interventions for the people living in extreme poverty to support treatment continuation. A monthly cash support of 1000 taka (12 USD approximately) per month during the course of treatment had been provided to cover nutrition and other related expenses. These patients also received additional support from the Ultra poor programme of BRAC to improve their livelihood.

**Results/Impact:** In the year 2019, a total of 10,646 TB patients started their treatment and received cash 15,022,975 support from the BRAC TB control programme for treatment support. The treatment success rate of the ultra-poor patient enrolled in 2018 was 98%, 385 cured, 143 completed treatment, one lost to follow up and six died.

**Conclusions:** Although TB related basic diagnosis and medicine is free of cost, provided by the NTP, the duration required to complete TB treatment is a challenge for the patients, especially those who are already under extreme poverty. Financial support for ultra-poor patients saves them from the catastrophic health care cost which also ensures treatment adherence and a better outcome.



### EP33-423-24 Gender-wise differentials in coverage of social protection scheme

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**Background and challenges to implementation:** Government of India launched a scheme for nutritional support - “Nikshay Poshan Yojana” (NPY) for all TB patients registered in the online portal “Nikshay” of National TB program. This scheme entails transfer of 500 INR every month throughout the course of treatment directly into the bank account of the beneficiary.

**Intervention or response:** Gender differences and inequalities play a significant role in how people of all genders access and receive healthcare. National TB programme has developed a National Framework for a Gender Responsive approach, which involves promoting active involvement of people affected by TB of all genders in all aspects of the design, planning and delivery of programmes. A gender-disaggregated analysis of the coverage of nutritional support incentives and the reasons for variations in coverage was studied.

**Results/Impact:** During the years 2018 and 2019, 64%, 66% and 64% of the Male, Female and trans-gender TB patients in the public sector received the NPY benefit ( $p<0.05$ ). A similar trend was observed across all State/UTs in the country, except for two States.

	Paid incentive	Not paid incentive	Total
Male	1376984	773024	2150008
Female	797376	402969	1200345
Transgender	1784	999	2783
Total	2176144	1176992	3353136

[Table.]

**Conclusions:** Gender differentials exist in provision of nutritional support scheme, favoring women TB patients. Implementation of measures to provide nutritional counseling to the person with TB as well as family, particularly for men and transgender persons with TB and ensuring timely availability of social support schemes to those eligible in order to ensure successful treatment outcomes and mitigate the socio-economic impact is the need of the hour.

### EP33-424-24 A nation-wide survey of cross-border referral assistance (or lack thereof) for TB patients in Japan

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**Background:** With ever-increasing population movement, systematic and effective cross-border referral to ensure continuity of care for tuberculosis (TB) patients who cross border during their TB treatment is critical. In Japan, approximately 1 in 10 foreign-born TB patients choose to continue their treatment outside Japan. However, the situation of assistance and referral for these patients has never been studied.

**Design/Methods:** A nation-wide survey was conducted with all public health centers which have experienced international transfer-out of TB patients between 2016 and 2017. The self-administered questionnaire survey consisted of 57 items on language assistance, referral coordination and post-departure follow-up. The data was analyzed descriptively.

**Results:** A total of 355 foreign-born TB patients had transferred out of Japan and the survey response provided data for 294 patients. Basic characteristics of the 294 patients are summarized in Table 1.

Gender	n	%	Country of birth	n	%
Male	165	56.1	China	67	22.8
Female	129	43.9	the Philippines	62	21.1
Age group (years)			Vietnam	54	18.4
0-19	9	3.1	Indonesia	46	15.6
20-29	174	59.2	Others	65	22.1
30-39	68	23.1	TB diagnosis		
40-49	23	7.8	Pulmonary TB	194	66.0
50-	20	6.8	Extrapulmonary TB	55	18.7
			Latent TB Infection	45	15.3

[Table 1. Characteristics of patients (n=294)]

Of the 294, 92.9% (n=273) received a face-to-face interview by public health nurses before leaving Japan. However, of the 273, Japanese language capacity of 50.9% (n=139) were rated as “poor” or “very poor” by the nurses. Yet professional medical interpreter was utilized only in 7 of 139 patients (5.0%). Referral coordination was attempted for only 21.6% of the 273 patients (n=59). Some of the reasons for not coordinating referral included; “did not know who or where to contact” (n=22), “had difficulty communicating with patient/family” (n=15), and “did not have sufficient time” (n=12). In terms of post-departure follow-up, treatment continuation and final treatment outcome were only confirmed for 11.4% (n=31) and 4.4% (n=12) of the 273 patients, respectively.

**Conclusions:** The survey revealed that foreign-born TB patients were potentially leaving Japan with sub-optimal information and education, and assistance in terms of referral and post-entry follow-up. In the light of this circumstance, we begun a cross-border referral project for foreign-born TB patients.

### EP33-425-24 Barriers to tuberculosis preventive therapy initiation in people living with HIV in Cambodia: patients and clinicians perspective

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**Background:** Effective management of latent TB infection (LTBI) is essential to reach the “End TB strategy” goals. In Cambodia, the current guidelines on LTBI management recommend TB preventive therapy (TPT) with 6 months of isoniazid monotherapy (6H) for people living with HIV (PLHIV) after exclusion of active tuberculosis. Nevertheless, only 21% of PLHIV newly initiating antiretroviral treatment received TPT in 2017.

The objective of this study, is to understand barriers driving low TPT initiation rates from health care workers (HCWs) and ART patients' perspectives.

**Design/Methods:** Focus group discussions (FGDs) were held in five provinces of Cambodia. A specific interview guide was used. Responses in Khmer language were transcribed and translated to English for analysis. An inductive thematic approach was applied to allow emergence of general themes.

**Results:** 30 PLHIV and 32 HCWs participated in 10 FGDs. Most of PLHIV did not know what LTBI was or if they received TPT. Nevertheless, some PLHIV attributed their side effects to this treatment: Nausea, headache, dizziness, tiredness affect their work and life stating they could not work and raise incomes for their families. They also explained the difficulty to take a treatment without TB symptoms but express a higher motivation to adhere to TPT when they received dedicated information.

For HCWs, most respondents said they don't prescribe because their patients complain about side effects and have concerns of poor adherence; also noting the long duration of 6H.

Additionally, most HCWs described previous experience of drug stock shortage, lack of trained staff on TPT, and old X-ray equipment.

**Conclusions:** Improving PLHIV knowledge of LTBI and generating demand for TPT will improve patient motivation. In addition, LTBI management should integrate dedicated regular HCW training and improved supply chain. Shorter treatments with less side effects may increase TPT coverage and adherence to treatment.

### EP34 TB: from bench to the bedside

#### EP34-426-24 Sensitivity of diagnostic tests in persons with abnormal chest radiographs

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**Background:** Peru has the second highest tuberculosis (TB) case burden in Latin America. To increase the detection of TB cases in high-burden communities, we piloted an active case finding intervention using mobile x-ray vans. Here, we describe the diagnostic characteristics of the individuals diagnosed with TB with this intervention.

**Design/Methods:** Between February 2019 and January 2020, in various locations in northern Lima, we stationed mobile units that offered free screening with chest radiography read with an CAD4TB automated detection system. Individuals with an abnormal x-ray result underwent a diagnostic evaluation comprising clinical assessment and sputum testing with Xpert MTB/RIF, smear microscopy, and culture. TB diagnoses were made by either an Xpert-positive result or based on chest x-ray findings and symptoms. We report the breakdown of TB cases by age, sex, and symptoms, and compare sensitivity of diagnostic test results.

**Results:** During 12 months, 391 individuals were diagnosed with TB; 388 had sputum samples processed by the lab. Sixty percent were male and the median age was 37 years. 79.1% of these TB cases reported having a cough within the last month and 13.1% reported no symptoms. 80.7% were positive by Xpert while 25.3% were positive by smear. Culture results were available for 319 (82.2%), of which 74.3% had positive cultures. All 98 individuals with positive smears also had Xpert-positive results. Six cases were culture-positive and Xpert-

negative, while 48 cases were Xpert-positive and culture-negative. Only 8.8% were diagnosed based on clinical findings alone (with negative results on all three diagnostic tests).

**Conclusions:** Xpert is much more sensitive than smear microscopy as a diagnostic test for individuals with abnormal chest x-ray. Notably, some cases are still missed by Xpert. TB should not automatically be ruled out in individuals with abnormal chest radiographs and negative sputum tests.

### EP34-427-24 Targeted intervention to strengthen treatment monitoring using follow-up sputum testing among ambulatory pulmonary MDR-TB patients in Xi'an, Western China

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**Background and challenges to implementation:** Sputum tests are essential for TB/MDR-TB diagnosis and treatment monitoring. However, as treated TB patients improve, they may experience difficulty producing sputum. Consequently, many TB doctors in China rely on chest radiography instead of sputum testing, even though evaluation of TB/MDR-TB treatment outcomes without sputum results can be difficult and unreliable. With support from the FHI 360 Control and Prevention of Tuberculosis (CAP-TB) Project, Xi'an Chest Hospital (XCH), a provincial-level hospital for MDR-TB in Shaanxi Province, China conducted targeted interventions to strengthen treatment monitoring through follow-up sputum tests among MDR-TB patients.

**Intervention or response:** Prior to the intervention, many TB patients did not submit sputum for follow-up testing according to protocol due to inconsistent physician requests and poor follow-up, and difficulties producing sputum. From August 2019, XCH began providing hospitalized MDR-TB patients with individual counseling, small-group thematic sessions, pamphlets and videos to make them aware of the importance of follow-up sputum tests and proper sputum induction techniques.

To ensure intervention accessibility for ambulatory patients, XCH implemented standard procedures with clearly defined roles and responsibilities. Before prescribing drug refills, TB doctors referred patients to a specially trained nurse counsellor, who directly observed patients collecting sputum. Airway clearance techniques were introduced, including stair-climbing, drinking hot water, chest wall percussion and sputum induction. The counsellor also provided sputum cups and instructions for safe home sputum collection.

**Results/Impact:** Prior to the intervention (May-June 2019), 106 (65%) of 163 ambulatory MDR-TB patients who attended treatment monitoring visits received sputum tests. From November 2019 to January 2020, 270

(81.8%) of 330 ambulatory MDR-TB patients submitted sputum - a significant increase over baseline. ( $\chi^2=16.998$ ,  $p=0.000$ ).

**Conclusions:** Targeted interventions significantly contributed to increased uptake of follow-up sputum testing among MDR-TB outpatients. XCH's experiences can be scaled-up to strengthen quality treatment monitoring at MDR-TB care facilities in China.

### EP34-428-24 Using Xpert among symptomatic people with negative sputum smear microscopy results in Maharashtra: a key to identifying missing TB patients

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**Background and challenges to implementation:** Sputum smear microscopy is the most common diagnostic test used in low and middle income countries, including India which represents 27% of the global TB burden. While it is simple to use and inexpensive, it has poor sensitivity. Novel diagnostic techniques, such as GeneXpert have been introduced but coverage is low due to limited accessibility in rural areas and high costs. Our study aims to evaluate the impact of increasing accessibility to Xpert testing on TB case notifications in Maharashtra.

**Intervention or response:** Our study was embedded in Ashakalp Healthcare Association's TB REACH intervention in 4 districts of Maharashtra. We retrospectively reviewed electronic patient records to identify all individuals with SS negative (SS-) results and abnormal chest x-rays (CXR) who were initially told that they did not have TB. Community health workers (CHWs) collected sputum samples from the identified individuals at their home and transported the samples to Xpert sites for examination. An Xpert machine was installed in one of the 4 implementation districts. CHWs were given a fixed salary, gas allowance and performance incentives for Xpert confirmation as well as treatment initiation.

**Results/Impact:** All samples were tested and an additional 167 persons with confirmed TB diagnoses were detected. Of these, 148 (89%) had abnormal CXRs and 19 (11%) did not have a CXR done due to inability to travel because of old age or pregnancy. This led to a significant increase in the notification of MTB cases in the project area compared to historical baseline.

**Conclusions:** Our results show that if access barriers are addressed symptomatic SS- patients are tested on Xpert, there is a strong possibility of identifying patients likely

to be missed by the health system. It is important to improve access to rapid molecular testing which are currently available only in urban settings while 67% of Indian population is still rural.

### EP34-429-24 Novel RNA markers of anti-tuberculosis treatment response

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**Background:** Current measurements of drug efficacy in tuberculosis (TB) clinical trials rely on the cultivation of the pathogen which is compromised when bacteria enter a non-replicating persist phase. Consequently, the effect of sterilising agents on the persist population is unmeasurable. We investigated a novel pre16S/16S rRNA ratio model to estimate the potential sterilising effect of high dose rifampicin (900 mg and 1200 mg) on persist bacillary population. In which during high dose rifampicin (900 mg and 1200 mg) treatment.

**Design/Methods:** Sputum samples from the phase 2/B high dose rifampicin clinical trial (HIGHRI2) were used to evaluate the model. The model uses de novo synthesis rate of pre-16S rRNA and 16S rRNA as markers of cell physiology and absolute bacillary load. Pre16S/16S rRNA ratios measured at different stages of in vitro bacterial growth were used to study the transition from an active replication to a metabolically less active stationary status as a potential pharmacokinetic-pharmacodynamic marker.

**Results:** A physiological response could be described by an exponential saturation curve of the following equation:

$$R(t) = (R_{\max} - R_0)(1 - \exp(-(\ln(0.01))/T t)) + R_0$$

By fitting such curve, we demonstrated that pre-treatment bacterial population was actively replicating however when treatment commenced there was a significant downshift in the metabolic activity of the bacteria. While 900 mg and 1200 mg rifampicin did not result in an improved early bactericidal effect, it suppressed RNA synthesis by 25 and 20 percent respectively. The maximum achievable suppression effect ( $R_{\max}$ ) of high dose rifampicin was significantly greater ( $p=0.0230$  and  $0.008$  in the 900 mg and 1200 mg arm, respectively) compared to standard therapy.

**Conclusions:** Our novel pre16S/16S rRNA ratio analysis model provides rapid, and accurate measurement of cell physiology and drug sterilising activity. It represents an innovative measure of drug efficacy and potential to accelerate pre-clinical and clinical trials of TB drugs.

### EP34-430-24 Low AUC/MIC target attainment of moxifloxacin during treatment of patients with MDR-TB in China

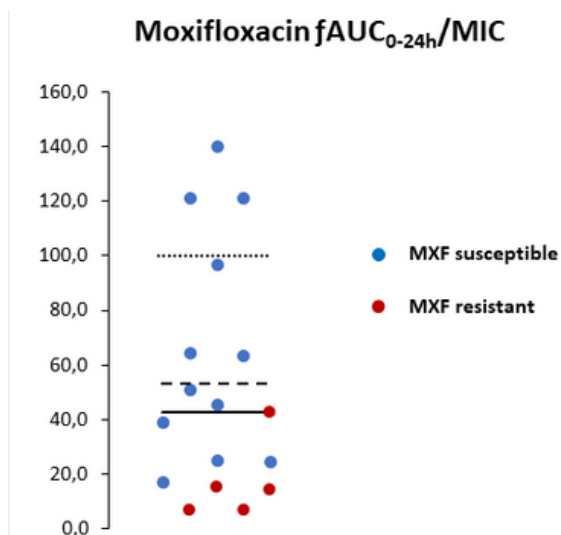
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**Background:** To combat multidrug-resistant tuberculosis (MDR-TB), there is a need for precision medicine where adequate drug exposure in relation to minimum inhibitory concentrations (MICs) are attained. The aim of this project was to investigate the target attainment of moxifloxacin (MFX), an essential MDR-TB drug.

**Design/Methods:** Consecutive patients with active MDR-TB were included in Xiamen, China and were treated on an empirical MDR-TB regimen according to national guidelines at the time of the study (2016-2018). Moxifloxacin was measured by liquid-chromatography tandem mass spectrometry (LC-MS/MS) in peripheral blood at 0, 1, 2, 4, 6, 8 and 10 hours post-dose at 2 weeks of treatment. Area under the concentration-time curve ( $AUC_{0-24h}$ ) was estimated by non-compartmental analysis. All isolates were subjected to phenotypic drug susceptibility testing (DST) for first- and second line drugs. MIC determination was performed with MYCOTB plate and *M. tuberculosis* H37Rv ATCC 27294 was included as a control in each test round.

**Results:** Patients ( $n=17$ ) had a median age of 29 years and 59% were females. MFX 400 mg daily was given to all patients. The median (range) MFX dose,  $C_{\max}$ ,  $AUC_{0-24h}$  and free ( $f$ )  $AUC_{0-24}$  (based on 50% unbound drug) were 7.7 mg/kg (5.9-9.5), 2.7 mg/L (2.0-3.8), 32.8 mg<sup>\*</sup>h/L (19.2-59.3) and 15.9 mg<sup>\*</sup>h/L (8.5-28.4), respectively. In total, 29% had a MFX resistant isolate and MFX MICs ranged from 0.125 to 4 mg/L. Overall, 82% (14/17) of patients, including the five patients with MFX resistant isolates, did not reach the  $fAUC/MIC$  target of >100, whereas only 35% (6/17) of all patients reached  $fAUC/MIC > 53$ .



[Figure 1. Individual drug exposure (area under the concentration-time curve, AUC) divided by the minimum inhibitory concentration (MIC) of moxifloxacin. The bold line represents the median and the dotted lines represent tentative literature-derived targets]

**Conclusions:** In this limited study, we noted a large variability in AUC/MIC for MFX during MDR-TB treatment in China and a very low target attainment of drug levels suggested in the literature. Therapeutic drug monitoring, in addition to higher dosing of moxifloxacin, should be used in MDR-TB regimens to optimize treatment.

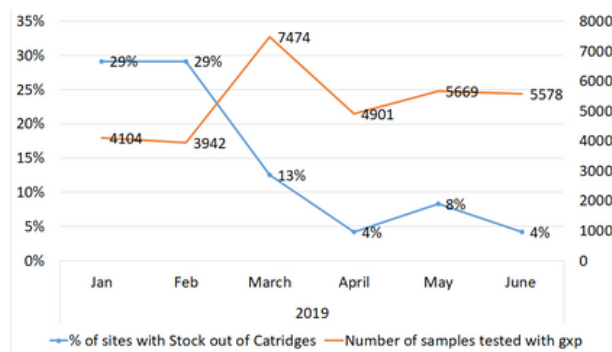
### EP34-431-24 Effective stock management of GeneXpert test cartridges in health facilities for uninterrupted tuberculosis laboratory diagnosis in three urban districts in Uganda

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**Background and challenges to implementation:** The World Health Organization (WHO) End TB strategy recommends that countries increase access to the Xpert MTB/RIF assay as an initial tuberculosis (TB) diagnostic test, including for rifampicin resistance. In Uganda, there are currently over 260 GeneXpert sites. However, access to testing is negatively affected by regular stock outs of GeneXpert cartridges because of poor stock management, untimely ordering of cartridges, and poor inventory records at health facilities. The USAID Defeat TB project worked with 24 facilities in Kampala, Wakis, and Mukono districts to reduce stock outs of Gen-

eXpert cartridges to improve access GeneXpert testing. **Intervention or response:** From January to June 2019, 24 of the 32 GeneXpert sites supported by the project in the three districts were purposively selected for the intervention. These facilities are reference laboratories performing GeneXpert tests on sputum samples from over 2,000 public and private facilities. The project supported these facilities' laboratory managers to improve management of their GeneXpert cartridge stocks by making reminder calls to facilities on supply order deadlines, conducting weekly reviews of stock cards for completion, and conducting biweekly inter health facility redistribution of cartridges based on average biweekly consumption rate and monthly physical counts.

**Results/Impact:** The number of GeneXpert tests performed increased by 26% between January (4,104) to June 2019 (5,578). There was also a reduction in the percentage of facilities with stock outs of cartridges from 29% in January to 4% in June 2019. Stocks were maintained across the facilities by redistributing from overstocked facilities.



[Figure. Number of facilities with stockout of GeneXpert cartridges and number of tests done]

**Conclusions:** Cartridge stock out is the most common factor affecting access and utilization of Xpert MTB/RIF assay as an initial diagnostic test and as a test for rifampicin resistance. We recommend proactive weekly stock analysis for action and reminders for ordering to address the gaps in genexpert Cartridges stock management.

### EP34-432-24 The efficacy of anti-tuberculosis therapy and treatment outcome are modulated by the magnitude of bactericidal activity on the rest of respiratory microbiome

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**Background:** Tuberculosis (TB) treatment requires a four-drug regimen for a minimum of six months. Some of the used antibiotics such as rifampicin (R) and moxifloxacin (M) are broad spectrum and may affect microbial ecology.

We investigated the impact of various anti-TB regimens on respiratory microbiome and how this influences patient treatment outcome.

**Design/Methods:** The microbiome of serial sputum samples from patients treated with either standard regimen Isoniazid-Rifampicin-Pyrazinamide-Ethambutol (HR600mgZE), HR900mgZE, HR1200mgZE, HR1500mgZE, HR1200mgZM, HR1200mgZSQ109(Q) or HR600mgZQ under high dose rifampicin and Multi-Arm-Multi-Stage trials were investigated over a 3-month treatment period. Patient sputum total RNA was reverse transcribed to cDNA and the 16S rRNA gene sequenced on Illumina MiSeq. Data processing and diversity comparisons between samples were analysed using Qiime 2.

**Results:** A total of 397 samples from 67 patients were analysed. The pre-treatment microbiome was dominated by Firmicutes (53%), Proteobacteria (13%), Bacteroidetes (13%), Actinobacteria (8%), Fusobacteria (4%) and *Streptococcus*(40%), *Neisseria*(9%), *Veillonella*(5%), *Prevotella*(4%), *Rothia*(1%).

On treatment, there was a displace-replace pattern with taxa such as Actinobacteria and *Mycobacterium tuberculosis* consistently cleared while others recovered. Culture conversion at week 8 of treatment was associated with 10% *Streptococcus* reduction compared to 3% for non-converters vis-a-vis 27% increase in those with indeterminate (contaminated) culture.

The majority (90%) of early culture conversions occurred in the HR1200mgZM group. The early bactericidal efficacy of the moxifloxacin regimen was reflected in significant reductions of amplicon sequence variant

(ASV) diversity ( $p=0.004$ ) and phylogenetic diversity ( $p=0.007$ ). HR1200mgZQ only reduced ASV diversity ( $p=0.014$ ).

Among the rifampicin regimens, only HR1500mgZE had significant reduction of ASV- and phylogenetic-diversity,  $p=0.027$  and  $p=0.006$  respectively.

**Conclusions:** Our findings suggest the efficacy of anti-TB therapy is modulated by its action on the rest of the respiratory microbiome. More insight into the microbiome-anti-TB drug interaction is crucial for informing improvement of TB treatment strategies.

### EP34-433-24 Impact of the human resource support scheme and sample transportation system on GeneXpert services in selected states in Nigeria: The KNCV/Challenge TB experience

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**Background and challenges to implementation:** Nigeria experienced a huge demand for GeneXpert test following its adoption as the initial diagnostic test for tuberculosis (TB). Despite the large number (398) of installed machines, utilization rate remained low. Reasons for underutilization included but not limited to human resource challenges and poor specimen transportation system (STS).

**Intervention or response:** To improve utilization of GeneXpert machines, KNCV/Challenge TB project, through USAID funding, implemented the GeneXpert human resource support scheme from 2016 to 2019. Courier model of STS was also implemented from 2016 to 2018 to facilitate the movement of sputum samples from health facilities and communities to GeneXpert facilities for TB diagnosis and prompt retrieval of results. A total of 20 ad-hoc staff were contracted across 9 states at the onset of the intervention in 2016, by December 2019, the total number of supported ad hoc staff providing GeneXpert services across 13 states rose to 55.

The courier model of STS was implemented through a local organization known as Riders for Health, to complement an existing hub and spoke model which had an inherent deficiency of limited coverage and poor response time.

**Results/Impact:** The average machine utilization in facilities with ad hoc staff rose from 39% at baseline to 123% in December 2019. Likewise, average machine utilization across facilities without ad hoc staff equally rose from 26% at baseline to 43% by the end of 2019. A total of 79,011 and 72,776 samples were transported in 2017 and 2018 respectively against 1823 transported in 2016. This demonstrated a 4234% increase over the baseline in 2017 and 3892% increase over baseline for samples transported in 2018.



**Conclusions:** The human resource support scheme significantly improved utilization of GeneXpert machines in supported facilities while the courier model of STS improved access to GeneXpert services especially among private entities like the patent medicine vendors and community pharmacists.

### EP34-434-24 Synthesis and evaluation of new compounds efficient against *Mycobacterium tuberculosis* isolates circulating in high-burden country, Russian Federation

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**Background:** *Mycobacterium tuberculosis* strains resistant to anti-tuberculosis drugs continue to circulate and present a global problem. Accordingly, a search for new anti-TB compounds is required. Russia is a high-burden country for multi- and extensively drug-resistant tuberculosis (MDR/XDR-TB), while primary MDR-TB rate is 25-30% across different regions of the country. Here, we performed synthesis of new compounds containing 2-aminobutanol moiety and tested their efficiency on *M. tuberculosis* clinical isolates from Russia.

**Design/Methods:** The target compounds were prepared from dimethyloxalate and (S)-2-aminobutanol or (R)-2-aminobutanol in refluxing methanol and were characterized by mass spectrometry, nuclear magnetic resonance, melting points and elemental analysis. The cell lines HEP-G2, HaCaT, HEK293 and CCL-1 were used to study the cytotoxicity and metabolism of tested compounds. The MTT colorimetric test was used to determine the average inhibitory concentrations of 50% (IC<sub>50</sub>).

The CFU test was used to assess the long-term antiproliferative effect of the compounds. In vitro antimycobacterial activity of all compounds was tested by resazurin microtiter assay (REMA). All compounds were tested against reference strain H37Rv and clinical isolates.

**Results:** The most effective (according to the results of testing on a laboratory strain H37Rv in two different laboratories) substances were tested on a panel of 30 clinical isolates of different genotypes (East Asian and Euro American lineages) and with different profiles of drug resistance.

The most efficient compound showed a wide range of MIC that varied from 3.1 µg/ml (H37Rv, some of clinical isolates) to 100 µg/ml (other isolates).

**Conclusions:** In view of the high diversity of MIC values, new anti-TB compounds should be evaluated with representative panels of clinical isolates representing different geographical areas and phylogenetic lineages and clusters of *M. tuberculosis*, especially in TB high-burden countries.

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### EP34-435-24 Improvement of elimination rate of *Mycobacterium tuberculosis* in sputum among patients receiving a bedaquiline and or linezolid containing regimens in Tanzania

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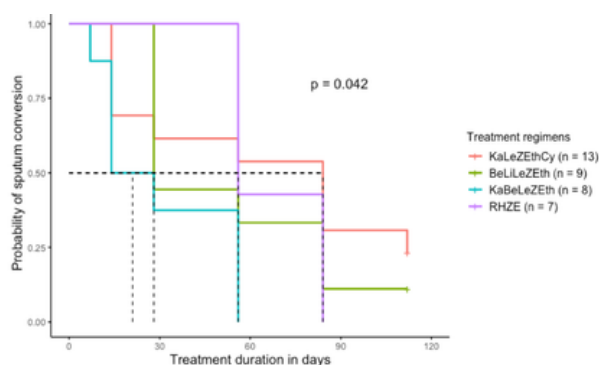
**Background:** The treatment of rifampicin or multi-drug-resistant tuberculosis (R/MDR-TB) has transitioned to injectable-free regimens. We deployed a molecular bacterial load assay (MBLA) to compare the elimination of *Mycobacterium tuberculosis* (MTB) in patients treated for either R/MDR or drug-susceptible (DS)-TB.

We hypothesized that MTB elimination rates and time-to-sputum conversion measured by MBLA are regimen-dependent.

**Design/Methods:** Serial-sputum samples from patients with R/MDR or DS-TB were processed at day-0, 3, 7, 14, and then monthly for 4-months of treatment. Treatment regimens were standard HRZE, all-oral R/MDR: Bedaquiline-linezolid-levofloxacin-pyrazinamide-ethionamide (BeLiLeZEth) and injectable: Kanamycin-(bedaquiline)-levofloxacin-pyrazinamide-cycloserine-ethionamide (KaLeZEthCy and KaBeLeZEth). MBLA quantified MTB 16S rRNA in sputum as estimated colony-forming-unit per mL (eCFU/mL). Patients who completed 8 treatment visits and had positive pretreat-

ment MBLA results were analyzed. Nonlinear-mixed-effects, Kaplan-Meier, and Cox-Hazard proportion models were used to estimate the MTB elimination.

**Results:** Thirty-seven patients who provided 296 serial sputa met the analysis criteria. The median (interquartile range: IQR) MTB elimination rate for 8, 9 and 13 patients who received BeLiLeZEth, KaBeLeZEth and KaLeZEthCy was 0.14 (0.13- 0.36), 0.26 (0.17 – 0.36) and 0.15 (0.14 – 0.17) log<sub>10</sub> eCFU/mL respectively. Median elimination in patients who received HRZE was 0.17 (0.08- 0.31) log<sub>10</sub> eCFU/mL and was similar to patients who received BeLiLeZEth ( $p = 0.568$ ). The median time-to-MTB elimination was shorter (21 and 28 days) in patients who respectively received KaBeLeZEth and BeLiLeZEth than other regimens (Figure 1, log-rank,  $p = 0.042$ ). In an adjusted Cox-model, hazard-ratios for MTB elimination were 5.33 (95% CI, 1.55 – 18.33;  $p = 0.008$ ) and 6.12 (95% CI, 2.08 – 23.52;  $p = 0.004$ ) for patients who received BeLiLeZEth and KaBeLeZEth respectively compared to KaLeZEthCy-regimen.



[Figure 1. Ka, Kanamycin; Be, Bedaquiline; Le, Levofloxacin; Li, Linezolid; Z, pyrazinamide; Eth, Ethionamide and Cy, cycloserine. KaBeLeZEth and the preferred all-oral MDR regimen such as BeLiLeZEth had the shortest time (21 and 28 days) to MTB clearance than RHZE (56 days) and the KaLeZEthCy (84 days). The preferred all-oral MDR regimen had shorter time to negativity than standard RHZE and injectable regimens, indicating its potential to shorten MDR-TB treatment duration to less than 9 months]

**Conclusions:** MBLA distinguished MTB elimination rate per regimen. Patients who received bedaquiline-containing regimens exhibited higher elimination-rates and shorter time-to-elimination. While testing this hypothesis in a large cohort of patients is recommended, an alternative oral-medicine would be needed to replace kanamycin.

## EP35 Ongoing battle against the tobacco industry

### EP35-436-24 Tier-based tax system benefitted tobacco industries in Bangladesh

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**Background and challenges to implementation:** Due to influence of British American Tobacco Bangladesh (BATB) and other Tobacco Industries (TI), existing tier-based tax system benefitted TI's and tax evasion became major obstacle on tobacco control. BATB is largest multinational tobacco industry owned more than 64% market share of tobacco in Bangladesh. Government of Bangladesh (GoB) and government owned different bodies has about 10% share and 5 high officials from GoB represents board of directors of BATB.

**Intervention or response:** Identify weaknesses, gaps and challenges of tax system for cigarettes and how existing system benefitted TI's, rather than the government. We have collected BATB's financial statements for from 2009 to 2018. Production of cigarettes, net-profit and annual tax submitted to government by BATB were analyzed to understand tier-based tax system for cigarettes and its effects on TI's net-profit and reduction of tobacco consumption in Bangladesh.

**Results/Impact:** In 2009, BATB's net-profit was 2,070 million BDT (US\$ 1 = 85 BDT at present) and net profit in 2018 was 10,010 million BDT. BATB's net profit boost-up about 5 times. While BATB's gross production of cigarettes increased only about 2 times, 24,701 million to 51,000 million sticks during this period. However, from 2017 to 2018, cigarette production reduces 3% whereas profit increased 28%.

One packet (10 sticks) premium brand cigarette MRP was 52 BDT (minimum) in 2010 with 58% supplementary duty (SD) and it increases 75 BDT in 2018 with 65% SD. Price is increased more than 44% (23 BDT) while tax increased only 12%. This gap in tax-system and increased prices benefitted BATB and their net-profit increased.

These findings shows that how BATB benefitted from the tier-based and complex tax system.

**Conclusions:** Cigarettes prices should increase with specific duty and single and uniform tax system should introduce in Bangladesh. National Board of Revenue should consult with tobacco

### EP35-437-24 Indoor and outdoor tobacco advertisements monitoring in Jakarta province 2019

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**Background:** Jakarta has adopted partial TAPS ban policy since 2015. The regulatory framework which governs this policy includes: 1) Bylaw No. 9/2014 concerning Advertising and 2) Governor Regulation No. 1/2015 concerning Outdoor Tobacco Advertising Ban. Following the enforcement of this policy, all registered tobacco billboards, banners, posters should be removed by end of 2016. However, the compliance of any tobacco control regulation in Indonesia remains low.

**Design/Methods:** This study use quantitative approaches. Data is collected through direct observation both for indoor and outdoor at 5 city/administrative areas. For outdoor, in each area the length of roads to be covered in the survey accounts for 20% of the total length of roads. For indoor, the total number of venues to be surveyed was 751 divided into 10 types of venues, i.e. shopping mall (n=122, 16%) restaurant (n=145, 19%), hotel (n=139, 19%), school (n=51, 7%), supermarket (n=67, 9%), traditional market, government office building, private office building, entertainment venue, and sports venue. For collecting data, this study use an android based mobile monitoring application.

**Results:** According to the results, a total of 20,8% indoor public places have tobacco advertisement in Jakarta. In indoor, the highest compliance was educational and sport places. The highest violence was found in supermarket and traditional market that reached to 79.1% and 80% respectively. In outdoor, we found 1,240 spots of tobacco advertisement. Most of the tobacco product advertisements are found in local road 65,8% and the lowest are primary arterial 0,2%.

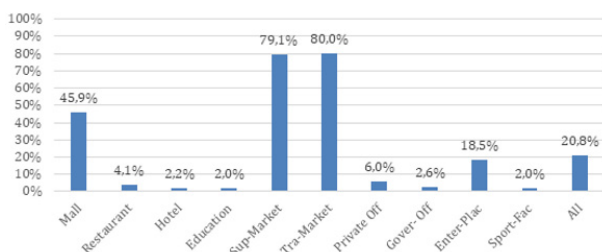


Chart 1. Distribution of indoor tobacco product advertisement according to types of venue

**Conclusions:** Tobacco industry massively used indoor venue to promote their deadly product after outdoor advertisement was banned in Jakarta. Point of sales was the most favorite channel to advertise tobacco products. Based on our study, a total of 80% modern and traditional market have tobacco advertisement inside.

### EP35-438-24 Strengthening tobacco control in Madhya Pradesh through integration of COVID and tobacco control

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**Background and challenges to implementation:** COVID has emerged as one of the greatest challenges in the history of mankind. There is evidence of tobacco consumption in spread of COVID infection. The COVID pandemic has given opportunity to tobacco control community for stronger enforcement and ban on tobacco products. Efforts made in Madhya Pradesh for effective tobacco control by integrating tobacco control measures with COVID.

**Intervention or response:** MPVHA took initiative in the state. Letters written and communication made with Principal Secretary, Commissioner Health, Mission Director at top level to ban use of tobacco to control COVID infection. Draft letters sent to District Collectors of 50 districts for ban on use of tobacco at public place, ban on sale of tobacco and ban on spitting at public places using different acts. Matter has also been discussed with the State & District Nodal Officers.

**Results/Impact:** Orders related to COVID and Tobacco have been issued in various districts. Different districts have used different acts to prohibit the use of tobacco, spitting of tobacco and sale of tobacco. Chief Minister has announced ban on sale of Gutka, Pan masala in the state. Urban administration department banned spitting at public places. A total of around 40 districts have issued orders using different section and acts. The orders can be divided into two types based on the acts used

1. District which have used IPC 268, 269, COTPA, Epidemic Disease Act 1897, MP Epidemic Disease COVID-19 Regulation, MP Public Health Act 1949. Districts prohibited use of tobacco in public places and spitting
2. Districts which have used Section 144, 188 of IPC. Districts prohibited sale of tobacco, prohibited use of tobacco and prohibited spitting.

**Conclusions:** Tobacco Control integrated with COVID control measures at state and district level resulted in strong tobacco control advocacy and increased the will of policymakers and implementers.

### EP35-439-24 Compliance assessment of electronic cigarettes online sales following a nation-wide ban of electronic cigarettes in India

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**Background:** India promulgated an Indian Ordinance on 18th September 2019 that prohibits e-cigarettes nation-wide. This study aimed to investigate the availability and characterise the internet electronic cigarettes (e-cigarettes) vendors (IEVs) that continued to sell vaping devices in India after the ban came into force.

**Design/Methods:** We conducted a structured internet search engine queries and used inclusion/exclusion criteria to identify IEVs. Subsequently, we performed a content analysis to all IEVs identified to check if they delivered vaping products to an Indian address (compliance with Indian Ordinance). The non-compliant IEVs were then described according to the characteristics of interest.

**Results:** Sixteen out of 45 IEVs (35.6%) were not compliant with the Indian Ordinance. Of all the non-compliant IEVs, half were general e-commerce, the majority (75%) did not apply any age verification methods, and few (43.7%) featured health or safety warnings on their websites. Many of the non-compliant IEVs employed a wide range of promotional strategies, such as price discounts, health benefits claims, and social networks utilisation.

**Conclusions:** E-cigarettes were still highly available and accessible in India through online sales following a bold step taken by the country to totally ban vaping products. Stronger law enforcement was warranted to ensure that vaping products will not undermine India's tobacco control achievements.

### EP35-440-24 Public Complaints against Violations of Smoke Free Area Regulations in the Capital Region Province of Jakarta in 2020

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**Background:** The smoking ban was stipulated in City Bylaw No. 2 in 2005 on air pollution control and was enhanced in Governor Regulation No. 75 in 2005 on smoke-free areas and Governor Regulation No. 50 in 2012 on the supervision, monitoring and law enforcement of smoke-free areas. The regulations were made to protect the entire community from the effects of smoking and also its substitute.

**Design/Methods:** Research team was collected 700 points of smoke free areas from the list which categorized as restaurant, hotel, mall, and entertainment places. Data collection was carried out by 7 enumerators spread on five administrative cities in the Capital Region Province of Jakarta. All data collected, whether or not they find a violation of smoke free regulations or not, must be inputted into the Smoke Free Jakarta application (android based). If the enumerator discovers a violation of the smoke free areas, it is required to report on the Twitter or QLUE application who provide by Jakarta Government.

**Results:** The results showed that there are violations of smoke free areas in Jakarta and only 110 out of 700 points are comply to the regulations. Based on the violation's category, the most violations occurred in smells of cigarette smoke (34%) followed by ashtray was found in the building (33,3%).

Administrative Cities Violations	East Jakarta n (%)	South Jakarta n (%)	North Jakarta n (%)	West Jakarta n (%)	Central Jakarta n (%)	Total n (%)
Smoking people was found	25 (12,1%)	42 (20,4%)	18 (8,7%)	69 (33,5%)	52 (25,2%)	206 (29,4%)
Designated smoking area inside the building was found	10 (4,3%)	25 (10,8%)	51 (22,1%)	95 (41,1%)	50 (21,6%)	231 (33%)
There is smoke free signed	80 (15,9%)	142 (28,2%)	82 (16,3%)	82 (16,3%)	117 (23,3%)	503 (71,9%)
Smells of cigarette smoke	29 (12,2%)	44 (18,5%)	40 (16,8%)	78 (32,8%)	47 (19,7%)	238 (34%)
Ashtray was found in the building	23 (9,9%)	51 (21,9%)	46 (19,7%)	70 (30%)	43 (18,5%)	233 (33,3%)
Cigarette butts was found in the building	21 (10,2%)	49 (23,8%)	9 (4,4%)	86 (41,7%)	41 (19,9%)	206 (29,4)

Table 1. Amount of Violations Based on Administrative Cities

**Conclusions:** Result showed that only 110 points of smoke free meet all the requirements from the regulation. Most violations were the smells of cigarette smoke (238 violations). Restaurant is the smoke free who have the highest number in all violation's category.

From 144 reports which has been made because of certain violation's category, only 3 of them had resolutions from the local government.

### EP35-441-24 Tobacco industry exploiting disaster situations to promote their image through CSR activities: an analysis of a series of cases in Sri Lanka

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**Background:** Guidelines on Article 5.3 and Article 13 of the World Health Organization's Framework Convention on Tobacco Control recommend banning Corporate Social Responsibility (CSR) activities including sponsorships by the tobacco industry. This study explored the CSR activities by the subsidiary of British American Tobacco (BAT), Ceylon Tobacco Company (CTC), which holds monopoly in manufacturing and sales of tobacco, during times of disaster in Sri Lanka in the post-FCTC-ratification era.

**Design/Methods:** This study is based on content analysis of media reports, websites, industry reports and photographs during the times of major disasters that happened in Sri Lanka from 2003 to 2020, namely, COVID-19 outbreak, the Easter terror attack, five floods, two landslides, one drought, the civil war and the tsunami. Thematic analysis was used to analyse the content.

**Results:** In 2020, during the COVID-19 outbreak, CTC attracted media attention for BAT vaccine's research and evidence from social media showed that they donated relief items during the curfew period. In 2018 and 2017, CTC donated relief items to flood victims in four districts and to drought affected families in tobacco cultivation areas in 2016. In 2010 CTC launched Sustainable Agriculture Development Programme targeting former members of Liberation Tigers of Tamil Eelam in a war affected area and reflected it as a part of the government rehabilitation programme. In 2005, CTC conducted a housing project for Tsunami victims. In the Tsunami period, CTC was reported to volunteer to collect data on the needs of the relief centers. There is no evidence of CTC's involvement in disaster relief for Easter attack in 2019, Meethotamulla landslide in 2017, Badulla landslide in 2014 and Flood disasters in 2015, 2008 and 2006.

**Conclusions:** CTC used disaster situations to promote its public image and gain political support via sponsorships and acts of philanthropy at national and grass root levels.

### EP35-442-24 Tactics of tobacco industry in defeating the proposal to ban single stick cigarette sales in Sri Lanka

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**Background:** The majority of smokers in Sri Lanka buy cigarettes in loose form. Global evidence indicates that singlestick cigarette sales promote smoking among the minors, the beginners and the poor due to high affordability and accessibility. In September 2018, Health Minister proposed to ban singlestick cigarette sales in Sri Lanka as recommended by the Framework Convention on Tobacco Control. The proposal failed to gain Cabinet approval, thus preventing its implementation. This study aimed to explore the tactics of the tobacco industry in defeating the proposal to ban singlestick cigarette sales in Sri Lanka.

**Design/Methods:** Investigative research techniques were used. Content analysis was carried out on identified government documents, media and industry reports in order to explore the tactics of the tobacco industry in the process.

**Results:** The strongest advocate against the ban was the Tobacco Retailer's Association (TRA), backed by the Ceylon Tobacco Company (CTC), the British American Tobacco subsidiary holding monopoly of cigarette sales in Sri Lanka. Their main argument was that it would impact retail business because of reduction in cigarette sales, affecting their livelihoods. TRA directly advocated to Minister of Finance (MoF) via a meeting. CTC further argued that ban would reduce the government tax revenue, which was amplified by media. MoF, at the Cabinet meeting that discussed the proposal, argued that ban would increase the use of beedi (a domestically produced cheap cigarette). Opposition to the ban by MoF and three other ministers, among the 30 members in the cabinet including the President and the Prime Minister, defeated the proposal.

**Conclusions:** CTC interfered and succeeded in defeating the proposal to ban singlestick cigarette sales in Sri Lanka. The main argument was such a ban would generate a negative impact, which was echoed by the TRA, the media and the MoF and three other ministers.

### EP35-443-24 Availability of tobacco products during the nationwide curfew period following the COVID-19 pandemic in Sri Lanka

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**Background:** Sri Lanka imposed a nationwide curfew from 20th March 2020 to control COVID-19 outbreak which lasted for approximate 8 weeks. This study aimed to explore the factors related to the availability of tobacco products during the period.

**Design/Methods:** Investigative research techniques were used to collect data. Written and photographic evidence from social media posts and web sites were reviewed and content was analysed using thematic analysis.

**Results:** Four public Facebook groups on tobacco smoking were identified to have been created exclusively during the curfew period. All four groups contained posts on experiences related to smoking and accessibility to tobacco products during the curfew. Brands, products and delivery services were advertised. PickMe, a local taxi service, and UberEats delivered cigarettes via their services, which are available online to deliver essential goods to homes.

Posts on smoking experiences showed a shift towards featuring available and/or cheaper brands; and, also, towards encouraging buying at higher prices ranging from 120% to 200%.

Mainstream media portrayed a picture of an increased demand for cigarettes by showing queued up retailers in front of provincial tobacco agents during each of the brief intervals of curfew-lifts.

During the same period, three counter measures were observed: Sri Lanka Police Department announced that an imprisonment up to 2 years is applicable for engaging in online sales and home delivery of cigarettes; a letter was sent to the President of Sri Lanka by nine stakeholder groups in tobacco control requesting to ban tobacco sales; and a public petition demanding a ban on tobacco sales, expecting 100,000 signatures, was initiated by a Facebook group supportive of controlling COVID-19 outbreak.

**Conclusions:** Amidst reduced availability of tobacco products during the curfew, mass and social media were used to promote tobacco products, violating the regulations on tobacco advertisement, promotion and sales in Sri Lanka.

### EP35-444-24 Tobacco Industry Targeting Ministers in Sri Lanka: Ministry of Finance 1977-2020

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**Background:** The Ministry of Finance is responsible for executing the government's economic policy in Sri Lanka. British American Tobacco's subsidiary Ceylon Tobacco Company (CTC) holds the monopoly of manufacturing and selling cigarettes in Sri Lanka. The proportionate government tax revenue from cigarettes is around 7% in Sri Lanka and estimated economic loss due to tobacco is around double the value of tax revenue. This study explores tobacco industry (TI) engagements of finance ministers (1977-2020) in Sri Lanka.

**Design/Methods:** Investigative research techniques were used based on the themes 'type of engagement' and 'TI investment'. News reports, online content, industry reports and community-level documentary evidence were used for content analysis.

**Results:** Nine individuals served as Finance Ministers during the period and the present Minister served twice in the post. Almost all had a history of direct engagement with CTC. The main engagement seen was obtaining sponsorship for government activities. One has a history of serving as a legal counsel to CTC. All were accused of not implementing a transparent tobacco tax policy and not increasing tax as recommended by the WHO. One requested a financial donation from CTC to Presidential Task Force on Drug Prevention in his budget speech. One attempted to import Chinese cigarettes and opposed the ban on single stick cigarette sales arguing that it will reduce sales and result in a reduction of tax revenue. Two Executive Presidents in Sri Lanka held Ministry of Finance portfolio themselves and both appointed CTC officials to government portfolios while they are holding CTC posts and intervened in implementing major tobacco control actions such as banning tobacco advertisements (in 1999) and implementing pictorial health warnings (in 2015).

**Conclusions:** Over the past four decades, tobacco industry has managed to engage Ministers of Finance in Sri Lanka and to successfully use them to affect serious policy related decisions.

## EP36 Molecular testing for TB infection and drug resistance

### EP36-445-24 Effect of switching from Xpert® MTB/RIF to Xpert® MTB/RIF-Ultra on tests done and tuberculosis cases diagnosed in Uganda: a case of assay superiority?

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**Background:** Uganda introduced Xpert® MTB/RIF assay into its TB diagnostic algorithm in January 2012. In July 2018, this assay was replaced with Xpert® MTB/RIF Ultra assay. We set out to determine the effect of this switch on tests done and TB cases detected in Uganda.

**Design/Methods:** This retrospective cohort study was carried out at 112 GeneXpert sites across the country. Data from the weekly GeneXpert programmatic reports were analyzed using Stata version 13. We compared the tests done and TB cases detected by Xpert® MTB/RIF and Xpert® MTB/RIF Ultra assays between Jan-June 2018 and Jan-June 2019 respectively. The outcome data were summarized into measures of central tendency and the association Xpert® MTB/RIF Ultra and Xpert® MTB/RIF was explored using a two-sided T-test which was considered significant if  $p < 0.05$ .

**Results:** A total of 128,476 (M: 1147.11, SD: 842.88) tests were performed with Xpert® MTB/RIF Ultra assay between Jan-June 2018, with 8,807 drug-susceptible TB cases detected (M:78.64, SD:52.29) and 144 (M:1.28, SD:3.42) Multi-Drug Resistant TB cases (MDR-TB). Whilst 107, 890 (M:963.30, SD: 842.88) tests were performed with Xpert® MTB/RIF assay between Jan-June 2019, 9,893 (M:86.54, SD:62.12) drug-susceptible TB cases were detected and 147 (M:131, SD:2.38) MDR-TB cases. The number needed to test (NNT) to get one TB case was 12 and 13 for Xpert® MTB/RIF and Xpert® MTB/RIF Ultra assay respectively. The difference between the two assays in terms of test performance ( $p=0.75$ ) and case detection both for susceptible TB ( $p=0.31$ ) and MDR-TB ( $p=0.95$ ) was not found statistically significant.

**Conclusions:** Conclusions: This switch didn't represent a case of assay superiority, there was no significant difference in test performance and overall case detection. The health systems approach should be used to elucidate all the probable potential of the MTB/RIF Ultra assay.

## EP36-446-24 Factors associated with drug-resistant tuberculosis among prisoners in São Paulo State, Brazil

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**Background:** Prisons are high-risk settings for drug-resistant tuberculosis because the prevalence of the tuberculosis is much higher than in the general population, regardless of it being a high- or low-income country. The purpose of this study to investigate the determinants of drug-resistant tuberculosis among prisoners in the state of São Paulo, Brazil.

**Design/Methods:** Retrospective cohort of drug-resistant TB cases for incarcerated people in São Paulo state, between 2006 and 2016. To analyze the determinants associated with drug-resistant TB, the backward method (likelihood ratio) was used, determining the adjusted odds ratio and respective 95% CI coefficients. Multiple models were proposed to adjust for potential confusion and interaction. The best fit model was selected based on the lowest Akaike information criterion coefficient.

**Results:** In total, 473 drug-resistant tuberculosis cases were confirmed among prisoners of São Paulo state. The majority were male, affected age range was  $\leq 39$  years, non-white and with less than eight years of education. The cases that presented negative results for sputum smear and sputum culture had, respectively, an ORa=0.65 (95% CI 0.52-0.82) and ORa=0.16 (95% CI 0.10-0.26) for drug-resistant tuberculosis in relation to the cases with positive results. The cases where the patient had AIDS and reported alcoholism presented, respectively, an ORa of 1.47 (95% CI 1.03-2.05) and ORa of 1.60 (95% CI 1.07-2.35) for drug-resistant TB. Individuals with a background treatment history for TB presented a stronger association with drug-resistant tuberculosis, ORa of 35.08 (95% CI 25.80-47.74).

**Conclusions:** Sputum smear, sputum culture, chest X-ray, AIDS, alcoholism and background treatment history for TB were determinants associated with resistance to antituberculosis drugs among prisoners. This is useful for the implementation of disease control measures related to the detection and monitoring of cases in the prison system. Confinement results in the rapid progression of the bacillus and increases treatment costs, directly affecting the Brazilian national health system.



### EP36-447-24 Did expansion of GeneXpert machines find missing TB patients? Experience from Nigeria

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**Background and challenges to implementation:** To address increasing need for GeneXpert as initial TB diagnostic test, USAID Challenge TB project (CTB) during 5 years installed 64 GeneXpert machines in public and private health facilities with additional 238 GeneXpert by other stakeholders. From 2011 to 2019, 407 GeneXpert machines (less than 45% geographical coverage across 774 LGAs) were installed; 130 (32.6%) installed in CTB supported LGAs. Starting from 2017, the TB program shifted emphasis to GeneXpert service optimization (47% utilization rate) and halted installation of more machines.

**Intervention or response:** CTB project introduced package of interventions geared towards creating demand for utilization of the GeneXpert services including engagement of Patient Medicine vendors and Community Pharmacists (PMVs & CPs); instituted sample transportation through courier and Riders for Health, "hub and spoke" health care worker, ad-hoc staff model and optimization of GeneXpert services through human resource (HR) support scheme.

**Results/Impact:** During PMVs/CP intervention, 95,676 presumptive cases were referred; tested 92,430 presumptive TB cases; notified 7,507 (8%) all forms of TB and commenced appropriate treatment. In 2018 alone, 72,776 samples were transported (3,892%) over 1,823 samples transported at baseline of which 6,980 (9.6%) TB cases were detected of the total samples transported. By engaging 53 laboratory ad-hoc staff, monthly test per GeneXpert machine rose from 130 (32%) to 294 (123%) at HR supported sites compared to 103 (43%) increase from 77 (32%) at non-HR supported sites. Support to "very high burden" GeneXpert sites with 2 ad hoc staff encouraged run of shifts and facilitated testing after working hours. The ad-hoc staff engaged increased testing yield from 738 to 1,502 (47%) across these facilities.

**Conclusions:** Adoption and scale up of GeneXpert machines as primary TB diagnostic tool is not enough to find all missing TB patients. Strategic package of interventions that create demand, ensure optimization and utilization of existing GeneXpert services should also be prioritized.

### EP36-448-24 Xpert MTB/RIF ultra improved the diagnosis of tuberculous meningitis in HIV-negative patients: a prospective study

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**Background:** Early and accurate diagnosis of tuberculous meningitis (TBM) is challenging. Xpert MTB/RIF Ultra (Xpert Ultra) might have high sensitivity, but its role in diagnosing TBM is uncertain, especially for HIV-negative cases. Implementation of Xpert Ultra in different epidemiological and geographical settings with different patient populations might gain different benefits. In this study, we evaluated the performance of Xpert Ultra for TBM diagnosis in HIV-negative patients in China.

**Design/Methods:** TBM suspected patients (e.g., headache, nuchal rigidity, altered mental status) were enrolled consecutively in 2 tertiary hospitals (Beijing Chest Hospital and Beijing Tiantan Hospital) from January 2017 to December 2018 in China. Their uncentrifuged cerebrospinal fluids (CSF) was subjected to smear, culture, Xpert and Xpert Ultra with 1-2ml CSF, respectively. The diagnostic performances of Xpert Ultra, Xpert and culture were evaluated against uniform clinical case definition and a composite microbiological reference standard. The differences of sensitivity and specificity between different diagnostic methods for TBM were tested based on the 95% confidence interval(CI).

	Culture	Xpert	Xpert Ultra
Reference standard: uniform clinical case definition %(95% CI; n/N)			
Sensitivity	18.42 (10.79-29.31, 14/76)	24.52 (16.91-34.02, 26/106)	44.34 (34.80-54.29, 47/106)
Specificity	100.00 (90.20-100.00, 45/45)	100.00 (90.20-100.00, 45/45)	100.00 (90.20-100.00, 45/45)
PPV	100.00 (73.24-100.00, 14/14)	100.00 (83.98-100.00, 26/26)	100.00 (90.59-100.00, 47/47)
NPV	32.70 (42.06-51.99, 14/107)	36.00 (27.75-45.12, 45/125)	43.27 (33.70-53.34, 45/104)
Reference standard: composite microbiological reference standard %(95%CI; n/N)			
Sensitivity	35.90 (21.68-52.85, 14/39)	49.06 (35.25-63.00, 26/53)	88.68 (76.28-95.31, 47/53)
Specificity	100.00 (90.20-100.00, 45/45)	100.00 (90.20-100.00, 45/45)	100.00 (90.20-100.00, 45/45)
NPV	64.29 (51.87-75.13, 45/70)	62.50 (50.26-73.40, 45/72)	88.24 (75.44-95.13, 45/51)

[Table.]

**Results:** In total, 151 patients were recruited, which included 32 definite, 55 probable, 19 possible TBM and 45 non-TBM patients according to uniform clinical case definition. Xpert Ultra produced a higher sensitivity than Xpert and culture, against uniform clinical case definition or a composite microbiological reference standard (table). Inclusion of Xpert Ultra outcomes increased the percentage of definite TBM case from 30.19% (32/106) to 50.00% (53/106). Both Xpert Ultra and Xpert accurately identified the one rifampicin (RIF)-resistant and the five RIF-sensitive cases defined by phenotypic DST. The specificities of culture, Xpert and Xpert Ultra were 100% (45/45).

**Conclusions:** Our preliminary results show that Xpert Ultra outperformed both Xpert and culture in terms of sensitivity for TBM diagnosis in the selected settings, which has the potential to help clinicians with TBM diagnosis.

### EP36-449-24 Hypothetical yield of serial tuberculosis screening using Xpert MTB/RIF among people living with HIV in Kampala, Uganda

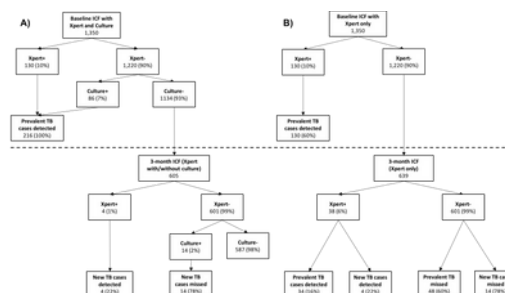
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**Background:** For people living with HIV (PLWH) living in tuberculosis (TB)-endemic areas, intensified case finding (ICF) for TB is recommended at every clinical visit. However, the yield of repeated ICF following baseline TB evaluation is unclear.

**Design/Methods:** We enrolled consecutive adults (CD4 $\leq$ 350 cells/mm<sup>3</sup>) initiating antiretroviral therapy (ART) from two HIV/AIDS clinics in Uganda from November 2014-December 2016. We performed Xpert MTB/RIF and liquid culture on sputum specimens collected at baseline and 3-month follow-up (for patients who did not initiate anti-TB treatment) to determine the burden of prevalent TB at baseline and 3-month incident TB. Using data from the scientific literature, we estimated the number of Xpert-negative prevalent TB cases who would have become Xpert-positive at 3-month follow-up. We then compared the yield of two potential strategies to detect Xpert- or culture-positive TB:

- 1) baseline ICF with Xpert and culture and 3-month ICF with Xpert only, and
- 2) baseline and 3-month ICF with Xpert only.

**Results:** Among 1,350 patients undergoing baseline ICF, 216 (16%) had Xpert- or culture-confirmed TB (Figure 1A). Of the 86 (41%) Xpert-negative prevalent cases, we estimated 34 (40%) would become Xpert-positive by 3-months. Repeat ICF was performed in 605/843 eligible patients; incident TB was diagnosed in 18 (3%), including 4 (22%) who were Xpert-positive. Thus, baseline ICF with culture and Xpert plus repeat ICF with Xpert only would detect 100% of prevalent cases and 22% of incident cases. Without culture at baseline, repeat ICF with Xpert only would detect 76% of prevalent cases and 22% of incident cases (Figure 1B).



[Figure 1. Yield of A) ICF with Xpert and culture at baseline and Xpert only at 3-months; and B) ICF with Xpert only at baseline and 3-months]

**Conclusions:** ICF is a crucial strategy for identifying TB among PLWH, but implementation is often challenging in resource-limited settings. In settings where culture is not available, repeat ICF with Xpert at 3-months will diagnose a substantial number of cases but would still miss 24% of all prevalent TB cases.

### EP36-450-24 Prevalence of gene mutations profiles by GenoType MTBDRplus in isoniazid Mycobacterium tuberculosis resistant strains, Tunisia 2015-2019

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**Background:** Global prevalence of isoniazid (INH) tuberculosis (TB) strains was 7.4% among new TB patients and 11.4% among previously treated patients during 2003-2017. Mutations in *katG* and *inhA* promoter are involved respectively in 93.2% and 21.4% of INH resistant strains (Dean et al., 2020).

The aim of this study is to determine the genetic profiles of INH *M. tuberculosis* resistant strains using the GenoType MTBDRplus assay V2.0 (Hain Lifescience, Germany).

**Design/Methods:** All INH resistant strains of *M. tuberculosis* (n=174), isolated during 2015-2019 in Tunisia, were used in this study. The phenotypic drug susceptibility

ty testing was performed by MGIT 960 or the proportion method on Lowenstein Jensen: 100 strains were multi-drug resistant (MDR), 23 INH mono-resistant strains and 51 INH poly-resistant isolates. All the strains were tested by GenoType MTBDR*plus* V2.0. For statistical analysis, *p* is considered statistically significant if it is <0.05.

**Results:** In this study, 82.8 % (n=144) of INH resistant strains showed mutations in codon 315 of *katG* gene, 10.9 % (n=19) had mutations in *inhA* promoter and 1.2 % (n=2) of strains presented a double mutations in *katG* 315 and *inhA* promoter. Mutations *katG* Ser315Thr and *inhA* C-15 T were the most involved in INH resistance and were found respectively in 82.1% and 11.5 % of INH resistant strains. Mutation *katG* Ser315Thr was strongly associated with MDR strains (*p*=0.0005<0.05). However, the substitution *inhA* C-15T was significantly associated with INH mono-resistant and poly-resistant isolates (*p*=0.0004<0.05).

According to the assay, 5.1 % (n=9) of INH resistant isolates did not carry any mutation in the target regions.

**Conclusions:** The majority of INH resistant strains in Tunisia presented mutations detectable by GenoType MTBDR*plus* (94.9%). This molecular identification of mutations could be useful to estimate the level of resistance to this drug (low, intermediate, high) and could, consequently, help to prescribe an adequate treatment.

### EP36-451-24 Evaluation of BD MAX MDR-TB for detection of Mycobacterium tuberculosis complex and mutations associated with rifampicin and isoniazid resistance

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**Background:** A rapid molecular test would decrease turnaround times for MTBC detection and prediction of antimicrobial resistance compared to current phenotypic methods that typically take several weeks or months due to the low MTBC growth rate. Early detection is crucial to allow early treatment of infectious patients, prevent spread of disease and reduce mortality. The aim of this study was to evaluate the clinical performance of the BD-MAX MDR-TB assay to detect rifampicin (RIF) and isoniazid (INH) resistance in MTBC.

**Design/Methods:** Forty-four clinical samples (10 sputa from patients with known mycobacterial infection and 34 DNA extracts from MTBC-positive patient specimens) were tested and results compared to both phenotypic and genotypic drug susceptibility test (DST) results using current in-house methods. DNA extracts from six MDR-TB, 3 RR-TB and 12 INH-mono-resistant TB isolates were included.

**Results:** BD MAX MDR-TB displayed excellent sensitivity (100 %) and specificity (100 %) for MTBC detection but lower sensitivity (76.3%) for *rpoB*, *katG* and *inhA* gene detection. Nine samples that gave MTB Low POS results (MTBC detected but resistance metrics were not measurable) had given in-house IS6110 PCR Ct values of >34 confirming low MTBC load. RIF and INH resistance determination showed 100 % agreement compared to current genotypic methods. High sensitivity and specificity was observed for RIF (100 % and 95.2 %) and INH (94.1 % and 100 %) resistance detection when compared to combined genotypic and phenotypic DST methods.

**Conclusions:** BD MAX MDR-TB offers sensitive detection of MTBC and associated resistance to RIF and INH in clinical samples. Results would be possible within the same working day with minimal staff time per sample. This provides an exciting approach to TB diagnostics potentially allowing for faster effective treatment of TB patients, particularly those with MDR-TB, thus limiting spread of disease.

### EP36-452-24 Culture positivity rates among Rifampicin resistant indeterminate patients tested using Xpert® MTB/RIF-Ultra in high TB/HIV care settings: Uganda case study

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**Background:** World Health Organization recommends additional testing using culture and Drug Susceptibility Testing (DST) methods for all patients initially tested with Xpert® MTB/RIF-Ultra technique and whose Rifampicin resistance pattern is indeterminate. However, the proportion of culture positive patients who would require a DST is uncertain.

The study sought to determine the culture positivity rate among Rif-Resistant indeterminate patients so as to inform national level planning of DST tests required for this patient category.

**Design/Methods:** This was a cross sectional study. A total of 75 patients tested using Xpert® MTB/RIF-Ultra from 22 districts across the country were included in this study. We extracted programmatic patient's data covering the period of June to December 2019 from the Laboratory Information System (LIS) based at National Tuberculosis Reference Laboratory (NTRL) into Microsoft excel 13.0 for analysis.

**Results:** The culture positivity rates among 75 patients (including 56 males and 19 females, median age: 39.7 years) with MTB trace detected, Rif-R indeterminate

(47) and MTB detected, Rif-R indeterminate (28) initial results were determined. The combined LJ and MGIT culture positivity rates among Rif-R indeterminate patients was 20%. The LJ and MGIT culture specific positivity rates were; 9% (7/75) and 19% (14/75) respectively. High positivity rates were however observed among patients with MTB detected, Rif-R indeterminate initial peripheral results (LJ culture [11%, 3/28], MGIT culture [25%, 7/28]) as compared to those with MTB Trace detected, Rif-R indeterminate initial peripheral results (LJ culture [9%, 4/47], MGIT culture [15%, 7/47]) respectively.

**Conclusions:** The overall LJ and MGIT culture positivity rate among Rif-R indeterminate patients tested using Xpert® MTB/RIF-Ultra was 20%. This would mean that phenotypic DST is possible for only 1 in 5 Rif-R indeterminate patients diagnosed with Xpert® MTB/RIF-Ultra. We recommend further studies to investigate the associated determinants of low culture positivity rates in similar settings.

#### EP36-453-24 A novel standardized artificial sputum for external quality control of the whole TB-diagnostic workflow

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**Background:** External quality assessment (EQA) monitoring standard TB-diagnostic procedures is essential for good laboratory performance. Currently there is no validated matrix for monitoring sputum-based TB-diagnostics including smear-microscopy, culture, and molecular testing. Since sputum is hardly obtainable and requires extensive pre-testing for Mycobacterium tuberculosis complex (MTBC) negativity, artificial sputum (AS) would be an alternative test matrix for EQAs.

**Design/Methods:** We have developed a novel mucin-based artificial sputum (MUCAS) suitable for molecular diagnostics. In this study MUCAS was macroscopically and microscopically compared to established AS based on methyl cellulose or polyacrylamide as well as to sputum. The performance of decontaminated MUCAS samples in mycobacterial MGIT and Löwenstein-Jensen (LJ) cultures was also investigated. For validating MUCAS in a clinical setting, we conducted an EQA trial including five partner laboratories in Tajikistan. The laboratories received a blinded panel of 20 MUCAS samples for LJ and MGIT culture with different H37Ra concentrations and negative controls. Samples were also analyzed in the Supranational Reference Laboratory Gauting (SRNL, Germany).

**Results:** In contrast to other AS, MUCAS macroscopically and microscopically resembled human sputum. After NA-LC-NaOH decontamination of spiked MUCAS samples high loads of MTB could be recovered and LJ as well as MGIT cultures could be subsequently performed. MTB survived for up to 13 days in MUCAS, which enables shipping of viable MTB strains to Tajikistan for EQA purposes: 4 of 5 and 2 of 5 labs had false positive and negative culture results, respectively. In one lab an extremely high MGIT contamination rate with was observed (14/20). No false positive results were obtained in the SNRL. 15% of MGIT cultures were contaminated and could not be analyzed. Auramine staining was only possible with high H37Ra concentrations.

**Conclusions:** MUCAS is suitable for EQA panels assessing Ziehl-Neelsen microscopy, mycobacterial culture and –as previously shown– molecular diagnostics.

#### EP36-454-24 The sensitivity and specificity of Xpert MTB/RIF Ultra in an active TB case finding setting and understanding the “trace call” result

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**Background:** The GeneXpert Ultra is a recent development to tackle the limitations of the MTB/Rif assay for diagnosis of paucibacillary TB. Interpretation of the “trace call” result is a challenge, especially when used in an active case finding setting. We evaluated the performance of Xpert Ultra against Mycobacterial culture and examined patient characteristics related to the trace call result.

**Design/Methods:** Between June-December 2018, consecutive patients 18 years and older, seeking routine health care services at the facility were approached for study participation. Consenting patients submitted two spot sputum samples that were subjected to mycobacterial culture, smear microscopy and Xpert ultra assay at the CIDRZ central laboratory.

**Results:** Of 804 enrolled, 794 submitted a sputum sample. The sensitivity and specificity of Xpert Ultra for smear-positive TB, was 98.0% and 33.3% respectively, while for smear-negative TB, sensitivity and specificity was 68.6 % and 95.3% respectively. A total of 38 “trace call” results were obtained. The odds ratios for “trace call” results were; sex 0.65(95% CI 0.33 -1.33), age 0.98 (95% CI 0.96-1.01), symptoms 1.03(95% CI 0.85-1.24), HIV status 1.06(95% CI 0.55-2.05) and degree of chest x-ray abnormality 1.01(95% CI 1.00-1.03).

**Conclusions:** In an active case finding setting, the sensitivity of Xpert Ultra for smear negative samples was comparable to that reported under passive case find-

ing. There was no patient characteristic associated with “trace call” results, therefore, decision to treat patients with “trace call” result in an active case finding setting should remain at the discretion of the clinician as per WHO guidelines for interpretation of “trace call” results. The low specificity of Xpert Ultra observed among smear positive was due to low number of smear positive culture negative samples included in the analysis.

## EP37 Joining efforts for TB elimination: the role of the private sector

### EP37-455-24 Is it worth investing additional resources to catalyze access to TB-care in private sector? An experience from Southern India

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**Background and challenges to implementation:** Despite being declared a notifiable disease since 2012, progress on private-sector TB notification in India hasn't reached estimated targets. Foundation for Innovative & New Diagnostics (FIND) India started implementing Joint Effort for Elimination of TB (JEET) project in late-2018 in collaboration with National TB Elimination Programme (NTEP) with support from The Global Fund in six provinces to enhance private sector engagement, promote standard TB care practices, access to microbiological confirmation & drug sensitivity testing (DST).

**Intervention or response:** Banking on existing “Hub-&-Spoke-model” of private health-sector, we deployed trained staff at identified health facilities to encourage TB notifications, uptake of microbiological diagnosis & universal-DST. Provider behavior was influenced by in-clinic-sensitization, providing linkage to free diagnostic & treatment services under public-sector. Selected health facilities (“JEET-Hubs”) manned by full-time staff “Hub-Agents” were serving nearby facilities termed as “Spokes” which usually were feeding/referring units of these hospitals/clinics. Hub-agents coordinated patient notifications, sample collection & linkage for diagnostic-testing while specially trained “Treatment-Coordinators” took care of treatment adherence till completion.

**Results/Impact:** Patient-wise notification data for 171 facilities (134 engaged & 37 not-engaged under project) was extracted from NTEP's web-based-portal “Nikshay” for Bangalore tri-city (Bangalore-Urban,

Bangalore-Rural & Bangalore-City) of Karnataka. Anonymized patient data was analysed using Microsoft\_excel & results were compared between engaged and not engaged facilities.

Study reveals that per provider annual TB notifications increased by 29% from 13.3% (2018) to 17.2(2019) in engaged facilities compared to 5% decrease (from 8.1 to 7.7) in non-engaged facilities. Engaged facilities reported seven-fold relative increase from to 2019 in microbiologically confirmed TB notifications compared with two-folds increase by non-engaged ones.

Type of hospital / clinic	Number of health facilities under review (n)	#of notifications (per provider notifications)		# & % of notified patients diagnosed based on microbiological confirmation	
		2018	2019	2018	2019
Engaged under project	134	1,778 (13.3)	2,308 (17.2)	122 (6.9%)	936 (40.6%)
Not engaged under project	37	299 (8.1)	284 (7.7)	22 (7.4%)	42 (14.8%)

[Table 1: Comparative trend analysis of private sector TB notifications by health care facilities (clinics & hospitals) engaged under JEET project in Bangalore, Karnataka (India) 2018 - 2019]

**Conclusions:** Additional resource investments like these project interventions have synergistic effects with existing interventions of the national TB programs (NTP). Research on qualitative aspects of private sector-providers and patient choices holds further scope for exploration.

### EP37-456-24 The importance of using systematic screening in high TB burden countries to improve case detection rates: a case from private clinical facilities in Nigeria

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**Background and challenges to implementation:** In high TB burden countries where 5-10% of patients seeking outpatient services have respiratory symptoms and 1-5% of these have TB, systematic screening is key to TB case detection. SHOP Plus implemented a model to increase TB detection through multi-cadre networks of private facilities across Lagos and Kano States. Clinical facilities, either hospitals or nursing homes, serve as network treatment centers. We compared screening, testing, and case-finding rates.

**Intervention or response:** We defined screening, testing, and case-finding rates, using a case-finding rate of 70% as a cutoff to classify facilities into high and low performance. Chi-squared tests compared categorical variables and regression analysis determined factors associated with higher case-finding rates using service delivery data from 542 clinical facilities from 2019.

**Results/Impact:**

- Median screening rate was higher in nursing homes (54.8%, 95% CI 44.3% - 66.0%) than hospitals (33.1%, 95% CI 28.2% - 39.3%) ( $p < 0.001$ )
- No difference seen in median testing rate of hospitals (90.4%, 95% CI 88.2% - 92.3%) vs. nursing homes (92.7%, 95% CI 86.1% - 96.2%) ( $p = 0.409$ )
- Nursing homes (27.9%, 95% CI 25% - 49.1%) had a higher median case-finding rate than hospitals (15.3% 95% CI 12.7% - 17.8%) ( $p < 0.001$ )
- 30% of nursing homes compared to 13% of hospitals had a case-finding rate above 70%
- The chance of having a high case-finding rate was 14 fold more in facilities with low outpatient department (OPD) volume than high OPD volume (AOR 14.3, 95% CI 3.8 - 54.5,  $p < 0.001$ ).

**Conclusions:** Facilities with low OPD volume had a higher case-finding rate, likely due to it being easier to systematically screen clients when the OPD volume is lower. A shortage in human resources for screening or low suspicion of TB may be responsible for the low case-finding rate in hospitals compared to community-centric nursing homes where OPD volume is typically lower. We confirm systematic screening is key to increasing case-finding rates.

### EP37-457-24 Private sector engagement in identifying TB cases in Bangladesh: BRAC experience and areas of improvement

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**Background and challenges to implementation:** Bangladesh has been one of the 30 high TB burden countries in the world with an estimation of 18% missing cases according to the World Health Organization (WHO). Several interventions have been taken so far to identify the missing TB cases in Bangladesh. The role of private health care providers has always been very crucial in this process. However, this engagement has to be improved for better programme achievement and impact.

**Intervention or response:** It has been very challenging to ensure the engagement of private health care providers in referring presumptive TB cases. BRAC TB Control programme, under the guidance of NTP has taken various initiatives to motivate private healthcare providers such as, Graduate Private Practitioners (GPP), non

Graduate Private Practitioners (non GPP), pharmacy holders, private hospitals, village doctors and others for increased referral of presumptive cases. Programme has mapped potential GPP and non GPP; established networking with them. GPP and non GPP have been oriented on TB services and a total 3,866 GPP and 5,070 non GPP received training in 2019.

**Results/Impact:** In 2019, a total 211,164 TB cases were identified in BRAC supported areas. Of these cases, GPP, government hospitals, and private hospitals referred 40%; Community Health Care Provider (CHCP) and Government Field Staff (GFS) referred 8%; Village Doctor (VD) and Non GPP referred 1%; and Shasthya Shebika (SS), TB patients, Self, Community Volunteer (CV) and others referred 51% cases.

Also, GPP, government hospitals, and private hospitals referred 244,389 presumptive TB cases; CHCP and GFS referred 10,526; VD and Non GPP referred 7,592; and SS, TB patients, CV and others referred 459,694 presumptive TB cases.

**Conclusions:** Private providers play a significant role and they need to be motivated for increased referral of presumptive TB cases. More effective and innovative intervention need to be implemented to increase participation of the private health care sector.

### EP37-458-24 Factors affecting Nigerian private health facilities' tuberculosis case finding performance: reviewing program data

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**Background and challenges to implementation:** Since October 2017, USAID's SHOPS Plus Nigeria program has engaged over 500 private hospitals and nursing homes in Lagos and Kano to increase TB case finding. Using data to adapt programming for improved performance, SHOPS Plus introduced systematic screening, community outreach, and a surge initiative in which select facilities receive screening support and oversight from experienced clinicians. SHOPS Plus support has led to a significant increase in private sector contribution to TB case finding in both Lagos and Kano States. In 2019, SHOPS Plus facilities identified 32% of the total TB cases identified in Lagos. To better target resources to private facilities willing to engage in active TB case detection, SHOPS Plus assessed the performance of its networked clinical facilities.

**Intervention or response:** We used data from 423 clinical facilities in Lagos and 119 in Kano from 2019 to determine screening, testing, and case-finding rates per facility and classified rates into good and poor performance (>75%). Regression analysis determined factors associated with good performance.

**Results/Impact:**

- 28% of facilities in Lagos and 35% in Kano had good performance ( $p=0.165$ )
- 50% of nursing homes compared with 22% of hospitals had good performance in Lagos ( $p<0.001$ ), facility type was not associated with performance in Kano ( $p=0.747$ )
- 64% of Lagos and 67% of Kano surge facilities had good performance compared with 26% of Lagos and 31% of Kano non-surge facilities ( $p<0.05$ )
- OPD attendance volume and availability of screeners were not associated with performance in either state ( $p>0.05$ ).

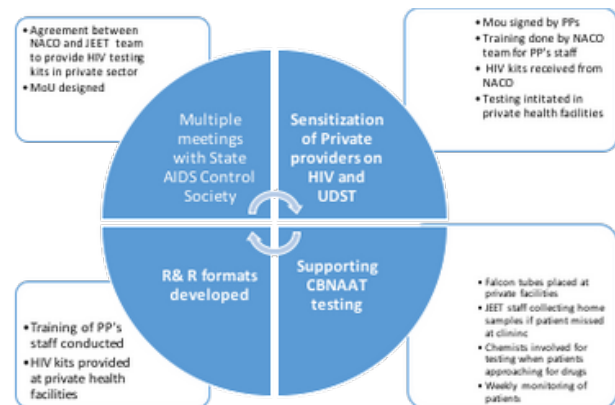
**Conclusions:** Different facility factors were associated with good performance in Lagos versus Kano. Being a nursing home or surge facility and conducting community outreach were associated with good performance in Lagos. Being a surge facility was the only factor associated with good performance in Kano. SHOPS Plus continues to adapt strategies based on data to achieve better performance across locations.

### EP37-459-24 Improving quality of care in private sector patients, State of Uttar Pradesh, India

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**Background and challenges to implementation:** One of the major thrust areas comprising the National strategic Plan of India (2017-2025) is effective engagement of the private sector to achieve Universal Access to TB Care. Centre for Health Research and Innovation (CHRI) is core Joint Efforts for Elimination of Tuberculosis JEET partner for implementing, The Global Fund to Fight AIDS, TB and Malaria (GFATM) supported private sector engagement in collaboration with National TB Elimination Program (NTEP), Government of India (GoI). JEET has successfully demonstrated quadrupling notifications in past two years and now working towards improving quality of care in private sector. Conducting Universal DST and HIV testing in privately-treated TB patients is both a problem and an opportunity for the JEET project in 15 high burden cities of UP. Access to CBNAAT testing to all private sector patients and simultaneously offering them HIV counselling and testing as per NTP guidelines is a challenge.

**Intervention or response:** JEET designed a system to provision NTEP offered CBNAAT and National AIDS Control Organization (NACO) offered HIV services to privately notified TB patients. The design is depicted below:



[Figure.]

**Results/Impact:**

- Proportion of TB patients with known HIV status doubled in 2019 as compared to 2018- 550349 (53%) with known HIV status as compared to 12443 (23%) in 2018
- UDST offered to 19513 (19%) patients in 2019 as compared to 2621(5%) in 2018

**Conclusions:** Effective advocacy with the private sector by civil society organization (JEET staff) and extending access to National TB and AIDS program services helped private sector to adopt quality services. Frequent joint program review need to be continued to ensure seamless supply of logistics.

To extend public health services in the private sector and ensure quality of care, NTP needs to build an ecosystem with an explicit framework that outlines interventions for collaborating with the private sector and earmark resources to support its execution.

### EP37-460-24 The experience of engaging private pharmacies in TB case detection in Ethiopia

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**Background and challenges to implementation:** Ethiopia missed over a third of estimated TB cases in 2018. A recent external program review identified failure to engage private health facilities as a missed opportunity. Out of over six-thousand private health facilities in the



country, only 6% are providing TB diagnosis and treatment services. Most of the services are limited to private hospitals and higher clinics to the neglect of lower level health facilities which are widely available in rural and semi-urban areas. We present an experience from an innovative project that engaged private pharmacies in Jimma Zone of Ethiopia.

**Intervention or response:** The project selected private pharmacies and drug stores in consultation with the regional health bureau, trained provides, and referral network was developed. Local volunteers were hired for each district and a local transport called Bajaj was organized to transport the referred presumptive TB cases. The documentation at the pharmacies/drug stores was checked and validated regularly. They maintained documentation about presumptive cases and recorded the results as and when (or if) they received. The treatment of all detected TB cases was in the public sector treatment centres.

**Results/Impact:** The project engaged 110 private pharmacies and drug stores. Of 33,626 people screened, 966 (2.9%) presumptive cases were identified, 947 (98%) consenting clients were referred to diagnostic centers, and 818 (86%) had arrived and tested of whom 60 confirmed patients were treated. The project also served as effective advocacy tool and raising publicity and attention amongst the TB managers and other stakeholders. Jimma zone detected 699 additional all forms of TB cases (21% increase) while notified cases declined by 38 in the control zone (1% decline).

**Conclusions:** This is the first experience of engaging pharmacies in TB case detection in Ethiopia. A more robust technical support and additional resources are needed for scaling up to other similar settings.

### EP37-461-24 The global fund public private mix TB grant: impact in three Southern states in Nigeria

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**Background:** The private sector constitutes a major part of the Nigerian healthcare system and serves most people. However, only 2.5% of these facilities are formally engaged for tuberculosis (TB) services contributing 11% to total case notification in 2017. To improve private sector engagement for TB services, The Global Fund grant for public-private mix (GF-PPM) was awarded in 2019.

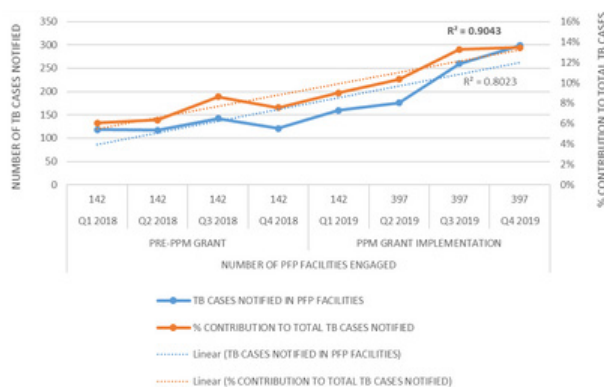
The grant runs a hub and spoke model where informal providers (spokes) such as patent medicine vendors, community pharmacists, and traditional birth attendants are linked to private hospitals (hubs) for identification of presumptive cases, referral and treatment of TB cases.

Although the GF-PPM project officially started in the first quarter, Q1 2019 with sensitization of various stakeholders, training and engagement of private-for-profit facilities (PFP) was conducted in Q2 2019. This study aims at assessing the coverage and contribution of the PFPs to the total TB case notification in the three DAHW-German Leprosy and Tuberculosis Relief Association (GLRA) supported States in Southern Nigeria.

**Design/Methods:** A retrospective desk analysis of TB case notification (2018-2019) from the 3 supported states was conducted. Total TB cases notified from PFP facilities and their percentage contribution to the total states' notification were computed against the number of PFPs. R2 was calculated.

**Results:** PFP coverage increased from 6% (142) in 2018 to 16% (394) with the engagement of 2637 informal providers linked to the hubs in 2019. In the same period, the 3 states had a 9% increase in TB case notification of which the PFP contribution increased by 44% (498 to 895).

The correlation between the case notification in PFP facilities, percentage contribution to total TB cases notified and number of engaged PFPs was significant at 0.9(90%) and 0.8(80%) respectively.



[Figure.]

**Conclusions:** Private sector engagement for TB services seems a promising approach to improving TB case-finding. Concerted efforts are required to address bottlenecks for optimal result.

### EP37-462-24 How frequent are TB care providers changed in the private sector in rural Bihar, India?

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**Background and challenges to implementation:** Contextual knowledge of the TB care pathway is crucial to improve the quality of TB care. The care pathway in the private sector is initiated by the patient and dependent on their own choices. Poor patient satisfaction can lead to

frequent change in providers, resulting in variable quality of care, high costs, and potential loss to follow-up. Understanding patient choices is crucial to improve TB care.

**Intervention or response:** We piloted a private sector engagement intervention from March 2017 to December 2019 in one block (pop. 208,000, 96% rural) of Samastipur district of rural Bihar, India. Its objective was improving outcomes for rural TB patients in private care via referral from physicians. A total of 23 physicians were mobilized to notify cases. Program staff visited participating physicians to collect details of diagnosed patients. Patients were counselled in-person by community health workers (CHWs) and on the phone by the program staff. CHWs also doubled up as treatment supporters.

**Results/Impact:** A total of 891 patients were notified. Out of these, 118 (13%) switched physicians at least once after diagnosis was established. Of 118, nearly 67% (79) changed their treating physician once, 24% (28) twice, and 7% (8) thrice. Two patients switched four times, and one changed five times. A total of 56 (47%) out of the 118 patients switched between the three prominent chest specialists in the region. Patients reported side effects and a lack of immediate relief in symptoms as important reasons for switching providers. It was also noted that physicians had little time for counselling.

**Conclusions:** A significant proportion of patients changed their providers during TB treatment for a variety of care concerns. Sensitizing physicians and patients have the potential to influence this behaviour.

### EP37-463-24 Initiation of preventive treatment among household contacts of TB patients registered at a private health care facility in Karachi, Pakistan

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**Background:** WHO recommends tuberculosis (TB) preventive treatment for household contacts for all individuals initiated on TB treatment. In 2018, at UN high-level meeting on TB, a target of 24 million household contacts to be started on preventive treatment was set. In 2019, preventive treatment was initiated for household contacts at a specialized TB diagnostic and treatment center in the private sector in Karachi, Pakistan.

**Design/Methods:** Between July 2019 to December 2019, all individuals registered on TB treatment were asked to refer their household members at a private TB care facility called "Sehatmand Zindagi (SZ) Center" located in

Nazimabad, Karachi, Pakistan, a low-resource high burden setting. TB screening was performed with Computer-Aided Detection for TB (CAD4TB) as triage tool for Xpert MTB/RIF testing. All individuals with CAD4TB score <60 were started on PET. Individuals with a CAD score >60 were tested on Xpert MTB/RIF and clinically evaluated.

**Results:** From a total of 375 index TB patients registered during the study period, 1066 household contacts were eligible for screening out of which 509 (47.7%) presented at the SZ center for evaluation. Of these 4 (0.4%) individuals were diagnosed with active TB and started on drug sensitive TB treatment for 6 months and 463 (43.4%) disease free contacts were started on 3HP (Table 1). In the two quarters, contact evaluation coverage improved from 30% to 70% and treatment initiation improved from 26% to 65%.

Indicators		Q3 2019	Q4 2019	Total
Eligible household members	A	597	469	1,066
Evaluated	B	181	328	509
Contact diagnosed with TB		1	3	4
Started preventive treatment	C	157	306	463
Treatment completed	D	56	53	109
Evaluation Coverage	B/A	30.3%	70%	47.7%
PT Coverage	C/A	26.3%	65.2%	43.4%
PT Completion Rate	D/C	35.7%	17.3%	23.5%
Overall Coverage	D/A	9.4%	11.3%	10.2%

[Table 1: House contact screening of TB patients for preventive treatment at a private health care facility in Karachi, Pakistan from July 2019 till December 2019.]

**Conclusions:** Improved patient counselling is required for greater evaluation coverage of household contacts and improved adherence of preventive treatment regimens in the private sector.

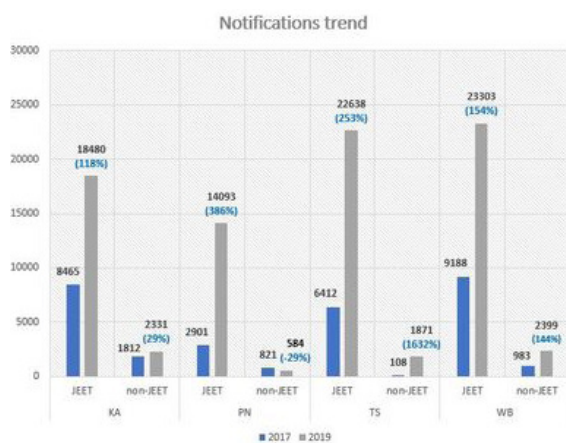
### EP37-464-24 Emerging trends in private sector notifications in India: experiences from Joint Effort for Elimination of Tuberculosis project

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**Background and challenges to implementation:** Engaging private sector is pivotal in achieving the target of ending TB in India by 2025. Foundation for Innovative New Diagnostics India (FIND) is implementing "Joint Effort for Elimination of Tuberculosis (JEET)" in collaboration with the National TB Elimination Programme (NTEP) and funding support from The Global Fund since 2018. The project is facilitating bacteriological confirmation by Xpert MTB/RIF, case notifications and treatment adherence.

**Intervention or response:** Government web-based portal (Nikshay) records for 2017 and 2019 were analysed for 89 project districts in 5 states (Andhra Pradesh, Telangana State, Karnataka, Punjab and West Bengal). Project was initiated in 2018 and by the beginning of 2019, activities were fully implemented. Data from 2019 has been compared with 2017 (baseline). The data were fully anonymized and Microsoft Excel was used for analysis.

**Results/Impact:** Overall, number of TB patients notified from the private sector increased by 147% (42,147 in 2017 to 1,04,249 in 2019). The notification rates doubled from 21 to 42 per 100,000 population. Number of private health facilities registered on NTEP's web-portal Nikshay, which notified any TB patient increased by 216% (2,809 to 8,875). About 31,697 patients were diagnosed microbiologically in 2019 compared to 6,767 in 2017. Compared with non-JEET districts within the same states (except AP where all districts are covered under JEET), there was an additional increase of 98% in JEET districts (191% vs 93%) (figure 1).



[Figure 1: notifications trend in JEET and non-JEET districts in 4 states of India (except AP as all districts are covered under JEET) (2017-19).]

**Conclusions:** It is evident that the project JEET has made significant gains in engaging the private sector in line with the NTEP's national strategic plan. Scaling up and sustaining these interventions will be critical in order to consolidate the gains made by the project.

## EP37-465-24 Establishment of TB diagnostic hubs in selected private laboratories

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**Background and challenges to implementation:** More than a quarter (27%) of people with TB symptoms seek care from individual private providers pointing to the unique role played by the private sector as key partners in TB control. As such, placement of an Xpert MTB/RIF in private laboratories to provide free TB diagnosis increases diagnostic access to the nearby chemists, private clinics and nursing homes who serve presumptive TB cases hence ensuring prompt diagnosis and cutting off the continuous transmission tap. Further, health providers manning these facilities benefit from tailored training, continuous mentor-ship and on-job supervision.

**Intervention or response:** Five diagnostic hubs in populated urban areas (Ruiru, Mavoko, Kiserian, Nakuru East and Kimini) were identified and equipped with the required infrastructure to offer fast-tracked TB diagnosis. A network of spokes was mapped around them and adequate referral and linkage mechanisms established using a reliable motorcycle riders.

Further, a web-based system was developed to ensure real-time and seamless communication between the hubs and spokes whenever a patient and/or sample was referred. The whole arrangement served to further enhance active case finding in both the hubs and spokes by ensuring the health providers had a high index of suspicion for TB.

**Results/Impact:** For the two quarters that the project has been ongoing; 36,434 number of people have been screened out of whom 1,684 were presumptive TB cases. 1,684 number of tests have been done with 9.2% yield of positive cases and a further 50 cases who were clinically diagnosed.

**Conclusions:** NTLDP has been a front-runner in implementing PPP activities for the past 20 year and is keen on interventions that help address critical gaps in the TB patient care pathway. As such, drawing on lessons learnt from this project provides a fertile ground to cascade the same to other areas with a high urban population and rich network of spokes.

## LATE BREAKER PRESENTATIONS WEDNESDAY 21 OCTOBER 2020

### OA-08 The Union student late-breaker session on lung health

#### LB-2092-21 Utility of previously identified host immunological biomarkers in the diagnosis of tuberculosis and monitoring therapy response in high and low endemic countries

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**Background:** New non-sputum-based tests are urgently needed for the diagnosis of Tuberculosis (TB). Many candidate inflammatory host biomarkers have been proposed but are yet to be validated in different demographic and ethnic settings. We assessed the performance of promising host biomarkers as tools for diagnosing TB in patients from a TB high-endemic compared to a low-endemic setting.

**Methods:** Plasma samples were obtained from presumed TB suspects recruited through longitudinal observational cohort studies at the Oslo University Hospital in Norway, and a health center in Cape Town, South Africa. Based on clinical and laboratory assessments, participants were classified as having TB or other respiratory diseases (ORD). The concentrations of 54 host biomarkers were evaluated using the Luminex multiplex platform and their diagnostic potential assessed by the receiver operating characteristic (ROC) curve with optimal cut-off values and associated sensitivity and specificity determined based on the Youden's index.

**Results:** Out of 185 study participants from both study sites, 107 (58%) had TB disease, and 78 (42%) ORD. Baseline levels of I-309, MMP-1, MPO, PDGF-BB, RANTES, CRP, Pentraxin3 showed diagnostic potential for TB in the Norwegian and South African cohorts, while I-309 was the most accurate single marker

irrespective of geographical setting. A combination of 4-markers (I-309+Procalcitonin+CRP+PDGF-BB) diagnosed TB among Norwegian participants with a sensitivity of 91.8% (95% CI, 83.8-96.6) and specificity of 89.5% (95% CI, 66.9-98.7) and a 3-marker signature (MMP-9+IP-10+sCD40L) performed in the South African cohort with sensitivity and specificity of 68.2% (95% CI, 45.1-86.1) and 88.8% (95% CI, 77.1-95.1) respectively. In all participants, a 5-marker biosignature (G-CSF+C3b/iC3b+Procalcitonin+IP-10+PDGF-BB) diagnosed TB with sensitivity and specificity of 72.7% (95% CI, 49.8 – 82.3) and 90.5% (95% CI, 69.6-98.8) respectively. Nineteen (19) biomarkers changed significantly by the end of treatment among Norwegian study participants.

**Conclusions:** Host plasma biomarkers showed diagnostic potential for TB irrespective of TB setting.

#### LB-1968-21 Characterization of clinical subtypes of antiretroviral therapy-associated tuberculous meningitis using host transcriptomic analysis

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 e-mail: carson.quinn@ucsf.edu

**Background:** Tuberculous meningitis (TBM) immune reconstitution inflammatory syndrome (IRIS), given its high mortality, is a feared complication of HIV-associated TBM. Unmasking IRIS can occur when antiretroviral therapy (ART) initiation unmasks previously undiagnosed TBM. Little is known about the clinical course or host immune response in patients with TBM presenting after ART initiation.

**Methods:** We prospectively enrolled patients presenting with definite, probable, or possible TBM (as defined by the uniform case definition) in Kampala and Mbarara, Uganda. We conducted a sensitivity analysis excluding those with the nonspecific categorization of possible TBM. We further grouped patients with CSF leukocytes >20 cells/mcL as inflammatory presentations potentially consistent with IRIS. Host immune response was characterized using differential gene expression analy-

sis of reads from next-generation sequencing of total RNA extracted from CSF. We interpreted differentially expressed genes using pathway analysis by open-source Reactome software.

**Results:** TBM was unmasked by ART initiation within 90 days prior to diagnosis in 17% (68/412) of the cohort. In this group, patients with inflammatory CSF had double the 14-day mortality of those without CNS inflammation (8/29 vs 5/39, Relative Risk 2.2, 95% CI, 0.8 to 5.9) despite similar baseline disease, a relationship not observed in ART-naïve or long-term ART cases of TBM. CSF RNA sequencing of nine cases each of inflammatory and non-inflammatory ART-associated TBM showed that those with CSF inflammation had upregulation of genes in pathways involved in signaling by interferon-gamma, Interleukin-12, and neutrophils.

**Conclusions:** This study suggests two distinct populations of ART-associated TBM patients exist: one with a paucity of CNS inflammation and relatively good prognosis, and one with significant CNS inflammation and poor prognosis. While the former group might be heterogeneous and include patients with other CNS infections or pathologies, the latter group could represent unmasking TBM-IRIS and is characterized by a host response with upregulated interferon and neutrophil pathways.

### LB-2082-21 Assessment of whole genome sequencing technology applied to drug-resistant tuberculosis diagnosis

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L.M. Villamayor,<sup>2</sup> M. Torres-Puente,<sup>1</sup> I. Comas,<sup>1</sup>

<sup>1</sup>Biomedicine Institute of Valencia, Tuberculosis Genomic Unic, Valencia, Spain, <sup>2</sup>Fundación para el Fomento de la Investigación Sanitaria y Biomedica, Genomics and Health, Valencia, Spain. e-mail: anamgmarin@gmail.com

**Background:** The constant rise and global spreading of drug-resistant tuberculosis is a major threat to Global Health. Drug susceptibility testing (DST) is the reference method for the diagnosis of resistances in *Mycobacterium tuberculosis*. However, this technique has significant drawbacks such as the requirement of complex infrastructure and expertise, a long period to obtain results and low accuracy and reproducibility for certain first-line drugs. In recent years, Whole Genome Sequencing (WGS) of *Mycobacterium tuberculosis* has emerged as a fast and reliable tool to predict the drug susceptibility profile of the bacteria.

**Methods:** We have performed a retrospective study of 735 isolates belonging to the Valencia Region (Spain) to assess the performance of WGS resistance prediction in a low burden setting. We compared our bioinformatics prediction with the phenotypic DST data to obtain the sensitivity and specificity. Additionally, we re-tested the clinical isolates with discordant DST-WGS results using the REMA assay.

**Results:** The results reveal a sensitivity of 85%, 73.3%, 50% and 52.38% for isoniazid, rifampicin, ethambutol and pyrazinamide respectively, and specificities ranging from 98.8% to 99.6%. The re-test data support a higher reliability of the WGS resistance prediction compared to the DST method but also highlight the necessity of expanding our catalogue of resistance-associated mutations.

First-line drug	Resistant strains using DST	Resistant strains using WGS	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy	Cohen's kappa
Isoniazid	40	39	85.00%	99.39%	89.47%	99.09%	98.57%	0.864
Rifampicin	15	14	73.33%	99.56%	78.57%	99.42%	99.00%	0.753
Ethambutol	12	10	50.00%	99.41%	60.00%	99.12%	98.56%	0.538
Pyrazinamide	21	20	52.38%	98.81%	57.89%	98.51%	97.40%	0.537

[Table.]

**Conclusions:** Our results suggest that WGS predicts drug susceptibility profile better than DST when the bacteria possess a common associated-resistance mutation. However, we need to expand our catalogue of rare mutations to improve our prediction analysis in terms of sensitivity. Our data also support the use of more than one critical concentration in DST, because the current breakpoints sometimes do not correspond with the clinical outcome. In conclusion, WGS is a promising tool to diagnosis first-line drug susceptibility that could be faster and more reliable than DST and would allow a better tailoring of treatments.

### LB-2115-21 Personalized adherence management in TB: using AI to schedule targeted interventions

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**Background:** This work addresses challenges in tuberculosis (TB) medication adherence for drug-sensitive patients in India. For support, patients are assigned a community health worker (CHW) who helps manage their adherence via basic monitoring and intervention. However, the CHW may manage as many as 200 patients simultaneously, making it challenging to target interventions to patients who need it most each day. Thus, we design an artificial intelligence (AI)-based system which learns to make intervention recommendations based on available resources and individual patient responsiveness to interventions over time.

**Methods:** We model the task as follows: Each day, each of N patients may or may not adhere to medication with some patient-specific probability. Due to limited resources, a CHW may only call k of those N patients

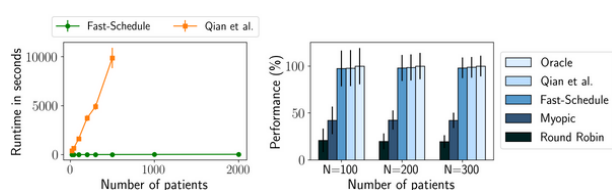


daily, whereby she learns their adherence and boosts their likelihood of adhering the next day. The CHW's goal is to maximize overall patient adherence over a 6-month-long treatment. We leverage AI tools such as 'Restless Bandits' to design a new algorithm, Fast-Schedule, to help CHWs solve this task, and compare to several baselines:

- 1) Round robin (current on-ground policy) - call patients in set order;
- 2) Myopic - greedy approach which maximizes the cohort's next-day adherence;
- 3) Qian et al. (state-of-the-art) - slow, mathematically near-optimal AI approach.

We evaluate each algorithm via simulation, using real-world adherence data derived from TB patients in Mumbai [Killian et al., 2019].

**Results:** All results are averaged over 50 independent trials. Our algorithm performs comparably with the state-of-the-art and runs exceptionally faster, while naive approaches underperform (Figure 1). Performance is scaled such that 100% corresponds to adherence achieved under a mathematical upper-bound "Oracle" and 0% to adherence when patients are never called.



[Figure 1]

**Conclusions:** Our algorithm's promising performance and fast runtime enables future pilots of intelligent planning assistants for personalized TB intervention scheduling (Killian/Mate, equal contribution.)

## LB-2119-21 Tale of the tape: use of mid-upper arm circumference (MUAC) to identify increased probability of pediatric TB treatment failure and mortality in a low-resource setting

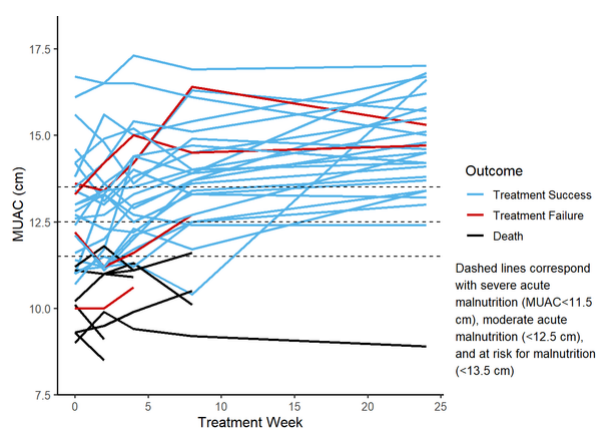
D. Van Aartsen,<sup>1</sup> S. Greenfield,<sup>1</sup> P. Rao,<sup>1</sup> M. Justine,<sup>2</sup> E. Mduma,<sup>2</sup> S. Mpagama,<sup>3</sup> E. Houpt,<sup>1</sup> T. Thomas,<sup>1</sup> J. McDermid,<sup>1</sup> S. Heysell,<sup>1</sup> <sup>1</sup>University of Virginia, Division of Infectious Diseases and International Health, Charlottesville, United States of America, <sup>2</sup>Haydom Lutheran Hospital, Haydom Global Health Research Centre, Haydom, United Republic of Tanzania, <sup>3</sup>Kibong'oto Infectious Diseases Hospital, Sanya Juu, United Republic of Tanzania. e-mail: djv3w@virginia.edu

**Background:** Malnutrition is common in undiagnosed pediatric tuberculosis (TB). A simple tape measure quantifying mid-upper arm circumference (MUAC) is ideally suited to identify malnutrition in low-resource and remote TB-endemic areas. Despite this, our understanding of how malnutrition measured by MUAC

is associated with suboptimal pediatric TB outcomes is limited. We hypothesized that lower MUAC at TB diagnosis and/or during treatment would be associated with poorer pediatric TB outcomes.

**Methods:** Rural Tanzanian children <5 years with drug-susceptible TB receiving first-line TB therapy were followed at diagnosis and 2, 4, 8, 24 weeks. Main outcomes were TB treatment outcome and mortality; analyses included simple and multivariate (adjusted for age, sex, presence of extrapulmonary TB disease, baseline hemoglobin, and symptom duration at time of diagnosis) logistic regression.

**Results:** In 41 children (median age=1.6 years; females=52%), the median MUAC at diagnosis=12.2 cm (IQR 11.0-13.3) and 41% were experiencing severe acute malnutrition (MUAC<11.5 cm). Figure 1 plots individual MUAC measures from TB diagnosis to treatment completion, and categorizes severity of malnutrition throughout treatment. In simple regression models, lower MUAC at TB diagnosis was significantly associated with both treatment failure (coefficient=-0.96, p=0.002) and mortality (coefficient=-1.47, p=0.004). Indeed, young children experiencing severe acute malnutrition were nine times more likely to fail TB treatment (95% CI=2.3-42, p=0.003) and 26 times more likely to die during treatment (95% CI=4.0-518, p=0.004). In multivariable models, lower MUAC at diagnosis was similarly associated with subsequent treatment failure (coefficient=-1.52, p=0.035) and mortality (coefficient=-1.76, p=0.018).



[Figure 1]

**Conclusions:** MUAC identifies young children with a greater probability of TB treatment failure or mortality. Given its applicability to low-resource settings where malnutrition and TB co-exist, MUAC can alert care-givers of specific pediatric TB cases in need of additional monitoring and clinical support in an effort to prevent negative TB outcomes.

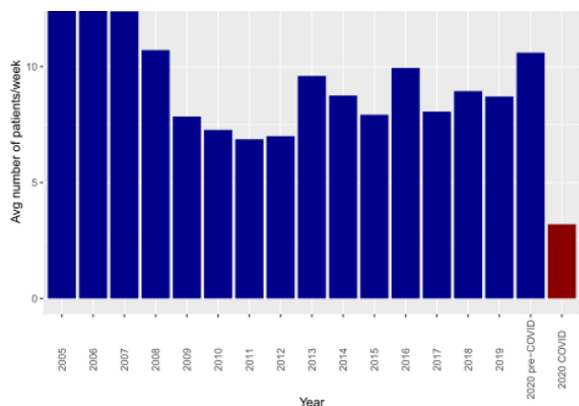
### LB-2047-21 Impact of COVID-19 pandemic on latent and active tuberculosis treatment registrations in Montreal, Canada: a retrospective study at the Montreal Chest Institute

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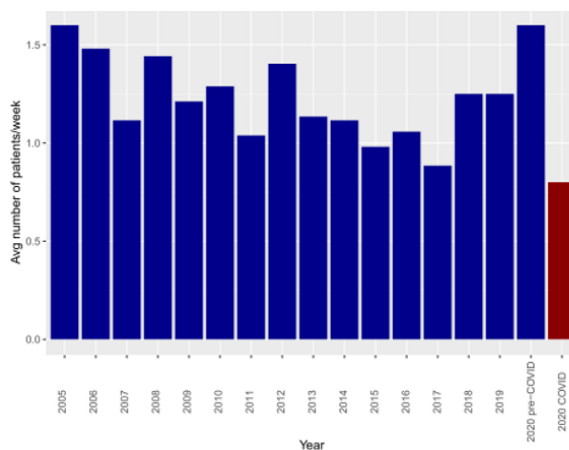
**Background:** We sought to assess the effect of the COVID-19 pandemic on registrations for treatment of latent tuberculosis infection (LTBI) or active tuberculosis at the Montreal Chest Institute (MCI), a specialized referral center in Montreal, Quebec, the city with the highest number of COVID-19 cases and deaths in Canada.

**Methods:** We used data from the MCI Tuberculosis Clinic E-Chart, in which all patients seen by our nurses to initiate LTBI or active tuberculosis treatment have been registered since November 26, 2005. Separately for LTBI and active tuberculosis, we compared the number of registrations per week since the COVID-19 public health emergency (“COVID era”) to the number per week prior to this (“pre-COVID”). We counted registration dates as COVID era if they fell within or after the week the Quebec government declared a public health emergency (Week 11 of 2020), and pre-COVID if they occurred prior. Using Poisson regression, we estimated rate ratios comparing rates of registrations (number registered per week) in the COVID and pre-COVID eras, adjusting for year, and week of the year.

**Results:** Between November 26, 2005, and June 23, 2020 (date of database query), we registered 6849 patients for LTBI treatment (6801 pre-COVID, 48 COVID era) and 902 for active TB treatment (890 pre-COVID, 12 COVID era).



[Figure 1a: Average number of LTBI treatment registrations per week in the pre-COVID era (blue), and the COVID era (red)]



[Figure 1b: Average number of individuals registered per week in the active TB treatment registry of the Montreal Chest Institute, by year. Blue: pre COVID era; Red: COVID era]

Figure 1(a) shows the average number of LTBI treatment registrations per week in the pre-COVID (blue) and COVID (red) eras, and Figure 1(b) shows this for active TB. Compared to pre-COVID, there was a 59% reduction in the registration rate for LTBI treatment during the COVID era (rate ratio=0.41 p<0.0001), and a 24% reduction for active TB treatment (rate ratio=0.76, p=0.37). **Conclusions:** There is an urgent need to implement strategies to mitigate the negative impact that the COVID-19 pandemic is having on LTBI and active TB management in Montreal, Canada.



## LATE BREAKER PRESENTATIONS THURSDAY 22 OCTOBER 2020

### OA-20 The Union late-breaker session on COVID-19

#### LB-2100-22 Comparative evaluation of the clinical accuracy of SARS-CoV-2 serological rapid diagnostic tests (RDTs) and manual ELISAs

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**Background:** Detection of SARS-CoV-2 specific antibodies is important to understand prior infection with this virus, which is responsible for the current COVID-19

Public Health Emergency of International Concern. RDTs enable testing at the point-of-care, where-as lab-based, more complex ELISAs enable higher throughput testing. With hundreds of antibody-detection immunoassays commercially-available, we aimed to evaluate the clinical accuracy of 10 RDTs and 15 ELISAs.

**Methods:** A multicentre study using archived serum/plasma was conducted in clinical laboratories across Brazil, Italy, Spain, Switzerland and the USA to assess the clinical accuracy of antibody RDTs and ELISAs. Positive samples came from individuals with a documented positive SARS-CoV-2 real-time-PCR test. Negative samples came from sick or healthy individuals, collected prior to September 2019. The overall sensitivity and subset according to days from symptom onset, and the specificity were determined. Results were compared to draft target product profiles developed by WHO that recommend antibody RDTs minimally have 90%/97% and ELISAs minimally have 95%/97% sensitivity and specificity, respectively. We also assessed the performance of each test using a reference panel (NIBSC, UK).

**Results:** 3/10 RDTs (IgM/IgG detection) met the sensitivity target ( $\geq 90\%$ : BTNX, SDBiosensor and Boditech) when tested on samples collected  $\geq 15$  days post symptom onset, and 5/10 RDTs met the specificity target ( $\geq 97\%$ ), with SDBiosensor being the only test meeting both targets. 11/15 ELISAs met both targets (sensitivity  $\geq 95\%$ , specificity  $\geq 97\%$ ), with the total antibody- or IgG-detection assays generally more accurate than the IgM- or IgA-tests. (Table 1).

**Conclusions:** The majority of RDTs evaluated are unable to meet global performance targets, with the exception of the SDBiosensor test; the majority of ELISAs do

RDT	Site 1: day 15+ Sens [95%CI], n	Site 1: Spec (95% CI), n	Site 2: day 15+ Sens [95%CI], n	Site 2: Spec (95% CI), n	ELISA (Switzerland)	Sens day 15+ [95%CI], n	Spec (95% CI), n
BIOMEDOMICS (USA, Italy)	85.8% [78.9%-90.7%], 134	95.8% [91.5%-98.0%], 168	80.0% [68.7%-87.9%], 65	97.4% [94.2-98.9%], 196	BEIJING WANTAI AB	100% [90.8%-100%], 38	98.8% [93.4%-99.8%], 82
					BEIJING WANTAI IgM	100% [90.8%-100%], 38	100% [95.6%-100%], 83
BTNX (USA, Italy)	96.3% [91.6%-98.4%], 134	83.6% [74.8%-89.7%], 168	87.3% [77.6%-93.2%], 71	95.3% [91.4-97.5%], 193	EPITOPE DX IgG	100% [90.8%-100%], 37	98.8% [93.3%-99.8%], 80
					EPITOPE DX IgM	81.1% [65.8%-90.5%], 37	98.8% [93.3%-99.8%], 81
INNOVITA (USA, Italy)	79.9% [72.3%-85.8%], 134	96.4% [88.2%-99.0%], 168	66.7% [54.7%-76.8%], 66	99.5% [97.2-99.9%], 196	EuroImmun IgG-S	97.4% [86.5%-99.5%], 38	98.8% [93.4%-99.8%], 82
					EuroImmun IgA-S	100% [90.8%-100%], 38	93.8% [86.4%-97.3%], 81
VIVADIAG (USA, Italy)	86.6% [79.8%-91.3%], 134	92.9% [87.0%-96.3%], 168	82.6% [72.0%-89.8%], 69	98% [94.9-99.2%], 196	EuroImmun IgG-N	100% [90.8%-100%], 38	98.8% [93.4%-99.8%], 83
SDBIOSENSOR (Brazil, Italy)	91.2% [86.7%-94.3%], 216	97.7% [93.3-99.2%], 128	89.9% [80.5%-95.0%], 69	99% [96.4-99.7%], 196	Novatec IgG	100% [90.8%-100%], 37	98.8% [93.4%-99.8%], 83
					Novatec IgM	67.6% [50.8%-80.9%], 34	100% [95.6%-100%], 83
					Novatec IgA	97.3% [86.2%-99.5%], 37	100% [95.4%-100%], 80
BODITECH (Spain)			96.3% [37.8%-99.9%], 70	91.4% [85.3%-95.1%], 128	Guangzhou DARUI IgG	100% [90.8%-100%], 38	97.6% [91.6%-99.3%], 83
					Guangzhou DARUI IgM	97.4% [86.5%-99.5%]	100% [95.6%-100%], 83
DYNAMIKER (Spain)			89.7% [68.5%-97.2%], 70	95.3% [90.2%-97.8%], 128	SDBIOSENSOR AB	100% [90.8%-100%], 38	98.8% [93.4%-99.8%], 83
HANGZHOU Alltest (Spain)			95.9% [70.1%-99.6%], 69	96% [91%-98.3%], 128			
INTEC. IgM/IgG (Brazil, Spain)	66.2% [59.7%-72.2%], 216	97.7% [93.3-99.2%], 128	89.6% [67.7%-97.2%], 69	95.3% [90.2%-97.8%], 128	TECOMedical IgG	100% [90.8%-100%], 38	55.4% [44.7%-65.6%], 83
					TECOMedical IgM	97.4% [86.5%-99.5%], 38	100% [95.6%-100%], 83
BIOEASY (Brazil)	70.8% [64.4%-76.5%], 216	95.3% [90.2%-97.8%], 128					

[Table 1]

achieve the targets. Further improvement of antibody RDTs is needed to enable decentralized serological screening. Additional research on which target antigen/isotypes correlate best with immunity are needed.

### LB-2093-22 Clinical accuracy, ease of use and limit of detection (LOD) of SARS-CoV-2 Antigen-detection rapid diagnostic tests

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**Background:** As of August 2020, over 21 million COVID-19 cases have been confirmed, however access to timely diagnosis is a persistent challenge world-wide, particularly in the Global South. Commercially available rapid diagnostics that detect SARS-CoV-2 antigens (Ag-RDT) have potential to enable fast and decentralized detection of infection.

However, the impact of Ag RDTs depends on their performance and ease-of-use (EoU) at the point-of-care. We aimed to evaluate six commercially available Ag-RDTs.

**Methods:** A multicentre, prospective study was conducted across COVID-19 testing centres in Brazil, the UK and Germany to assess the clinical accuracy of Ag-RDTs in persons presumed to have COVID-19 compared to routine RT-PCR. All Ag-RDTs were performed using a nasopharyngeal and/or oropharyngeal swab, following the manufacturers' instructions for use.

Results were compared to a draft target product profile developed by the WHO that recommends Ag-RDTs meet minimally 70%/97% and optimally 80%/99% sensitivity and specificity, respectively. Analytical sensitivity was determined using standardized dilutions of the SARS-CoV-2 isolate REMRQ0001/Human/2020/Liverpool propagated in Vero E6 cells. A System Usability Scale (SUS) questionnaire and EoU assessment were filled by at least 3 operators per test.

**Results:** Clinical performance varied widely: <50%-89% for sensitivity, and 87-100% for specificity. STAN-DARDQ demonstrated the best overall performance: 76.6%/99.3% sensitivity/specificity in Germany, and 88.7%/97.6% in Brazil. 2 tests met the proposed minimal WHO sensitivity target and 3 met the minimal specificity target. Analytical and clinical sensitivity were

consistent, except for Respi-Strip, (albeit with a low sample size). EoU also varied with SUS scores ranging from 54-86 (Table 1).

Test Name	Sensitivity (95% CI)		Specificity (95% CI)		LOD (test-specific swab/buffer)	Ease of Use
	Germany +/- UK	Brazil	Germany +/- UK	Brazil		
Bionote, NowCheck	ND	69.2% (55.7-80.1)	ND	87.4% (81-91.9)	TBC	TBC
Coris, Respi-Strip*	50% (15-85)	ND	95.9% (93.1-97.6)	ND	1 x 10e4 pfu/ml	54 out of 100
Rapigen, BIOCREREDIT	38.5% (17.7-64.5)	TBC	100% (99.5-100)	TBC	5 x 10e4 pfu/ml	TBC
SD Biosensor, STANDARDQ	TBC	75.4% (63.3-84.5)	TBC	97.5% (94.3-98.9)	2.5 x 10e4 pfu/ml	TBC
SD Biosensor, STANDARDQ	76.6% (62.8-86.4)	88.7% (81.2-93.4)	99.3% (98.6-99.6)	97.6% (95.2-98.8)	5 x 10e3 pfu/ml	86 out of 100
Shenzhen Bioeasy, FIA*	66.7% (41.7-84.8)	ND	93.1% (91-94.8)	ND	TBC	73 out of 100

\*clinical studies stopped early due to low specificity

ND = not done; TBC = to be confirmed; LOD = limit of detection

[Table 1.]

**Conclusions:** Our results suggest that though there is substantial variability between tests, at least two Ag-RDTs meet WHO targets. Given the fast turn-around-time and usability at POC, these tests are likely to have clinical utility despite imperfect sensitivity, however further research and modelling is needed to assess Ag-RDTs' impact.

### LB-2090-22 High mortality among persons with co-morbid rifampicin-resistant tuberculosis and COVID-19 in Khayelitsha, South Africa

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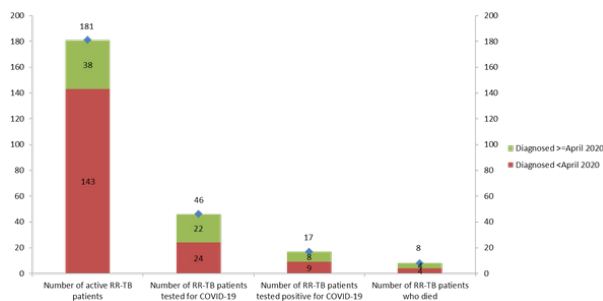
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**Background:** The Western Cape of South Africa has high rates of HIV and tuberculosis, including rifampicin-resistant forms (RR-TB), and was the initial COVID-19 hotspot in South Africa. There are limited data describing the COVID-19 pandemic among persons with RR-TB.

**Methods:** From April 2020, PCR based COVID-19 testing was initiated in Khayelitsha, South Africa; testing criteria for COVID-19 changed from testing based on

a positive contact or travel history, to symptom-based testing, and finally to risk-based testing over the study period. We conducted a retrospective cohort study of all active RR-TB patients to determine those who were tested for COVID-19 from April 2020-July 2020. We describe the COVID-19 cascade of care.

**Results:** As of April 2020, there were 181 active RR-TB patients on treatment of which 177 (66%) were known to have HIV; 38 (21%) of these patients were diagnosed with RR-TB from April 2020 onward (Figure 1). Overall, 46 (25%) RR-TB patients were tested for COVID-19, 22 (48%) of whom were diagnosed from April 2020 onward. Among the 42 RR-TB patients tested for COVID-19, eight were tested for COVID-19 prior to being investigated for TB; the median time from COVID-19 investigation to RR-TB diagnosis among these patients was 7 days (interquartile range [IQR] 2.5-7.5). The remaining 35 patients were investigated for COVID-19 a median of 3.0 months (IQR 1.4-11.3) after their RR-TB diagnosis. Overall, 17 (37%) RR-TB patients tested COVID-19 positive. Among the patients with RR-TB and COVID-19, eight (47%) died; one of these patients was hospitalized prior to death. The median time from COVID-19 diagnosis to death was 2.5 days (0-25.5).



**Conclusions:** Few patients newly diagnosed with RR-TB were investigated for COVID-19 at baseline suggesting missed opportunities to detect COVID-19 in this high risk population. Additionally, the mortality was high in this dually infected population.

### LB-2122-22 Tuberculosis and COVID-19 Co-infection among people with cough screened during the active case finding of COVID-19 in community with a high prevalence of tuberculosis

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**Background:** Information on the prevalence of tuberculosis (TB) and COVID-19 co-infection is limited. Knowing the prevalence of this co-infection in a population with a high incidence of TB is the objective of this study.

**Methods:** The intervention was realized in the north of Lima in the jurisdiction of Regional Dependence of Peruvian Ministry of Health (MoH) as part of the activities of COVID-19 response. Any person who reported cough during the active case finding activities for COVID-19 was invited to provide a sputum sample after taking the nasopharyngeal swab to rule out COVID-19. The nasopharyngeal swab and sputum samples were obtained by a field team of Socios En Salud (SES) as in known Partner in Health in Peru and processed in the molecular laboratory of SES in Carabayllo, Lima, Peru. The nasopharyngeal swabs were processed by SARV-CoV-2 PCR Test and sputum samples by the Xpert MTB/Rif Ultra test.

**Results:** From 966 persons who were screened by COVID-19, 322 (33%) of 966 persons had a SARV-CoV-2 PCR Test positive and 126 (13%) reported to have a cough. From these 126 persons, 2 (1.6%) had Xpert MTB/Rif Ultra positive which means a TB incidence of 1587 per 100000 inhabitants. These 2 persons had a SARV-CoV-2 PCR Test negative (Table 1).

	SARV-CoV-2 PCR Test Positive	SARV-CoV-2 PCR Test Negative
Xpert MTB/Rif Ultra Positive	0	2
Xpert MTB/Rif Ultra Negative	48	76

[Table 1. Comparison between SARV-CoV-2 PCR Test and Xpert MTB/Rif Ultra]

**Conclusions:** The implementation of active case finding of TB among people screened for COVID-19 in communities with a high incidence of TB is needed. The prevalence of TB/COVID-19 co-infection is not common in this population.

### LB-2113-22 Automated detection of COVID-19 in chest x-rays using deep learning for instant triage in hospital settings and integration with structured report generation

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**Background:** We developed deep learning (DL) models for detecting COVID-19 in chest x-rays (CXR) with "Human Expert in the loop" which also yielded a radiologist validated report. We report the model performance, clinical observations, challenges faced while building DL models. We observe that our model performs at par with imaging experts when compared to RT-PCR test results (ground truth), hence can potentially be used in hospital-based scenarios.

**Methods:** Retrospective study performed in a prominent Hospital, Mumbai, India. The analysis included 3180 patients (9098 CXR), with RT-PCR results for 604 patients

(1656 CXR): 484 positive and 120 negative. Expert radiologists annotated CXRs for classical COVID patterns: airspace opacities, ground-glass opacities/consolidation; primarily bilateral/peripheral, prominent in lower zone. Our DL models were tested on this out-of-sample data. The architecture consisted of two models, one (7 million parameters) categorized image COVID positive or negative and another (36.4 million parameters) predicted the infected region. The outcome was decided on aggregate decisions from both models. This output was referenced to British Thoracic Society of Radiology’s Covid-19 structured reporting module classifying CXRs: classic, probable, indeterminate, or unlikely.

**Results:** The model demonstrated sensitivity of 0.67, 95% CI[0.59,0.74], specificity of 0.43, 95% CI[0.26,0.41], with accuracy 0.5, 95% CI[0.46,0.55], whereas imaging experts’ showcased sensitivity of 0.38, specificity 0.52 with accuracy of 0.47. The model outputs assisted in generating semi-automated structured radiology reports (SRR), significantly reducing the expert’s efforts to finalize auto-generated SRR reports with minor modifications.

Metric	Radiologist	95% CI	AI	95% CI
Sensitivity	0.38	[0.31, 0.46]	0.67	[0.59, 0.74]
Specificity	0.52	[0.47, 0.57]	0.43	[0.26, 0.41]
Precision	0.27	[0.22, 0.33]	0.36	[0.3, 0.41]
Accuracy	0.47	[0.43, 0.52]	0.5	[0.46, 0.55]
F1-score	0.32	[0.26, 0.38]	0.46	[0.41, 0.52]

[Table.]

**Conclusions:** Recognizing high false-negativity in antigen tests, expenses, time required for RT-PCR results; finding parallel alternative methodology for early COVID-19 diagnosis in symptomatic patients is imminent. This can add immense value in hospital-based practices, where suspected CXR studies can be triaged instantly. This can support prompt attention for symptomatic patients, isolating probable suspects, assisting timely treatment, consequently curb community transmission, and minimize stress on healthcare systems.

**LB-2051-22 Potential impact of COVID-19 pandemic on essential tuberculosis services in Sri Lanka**

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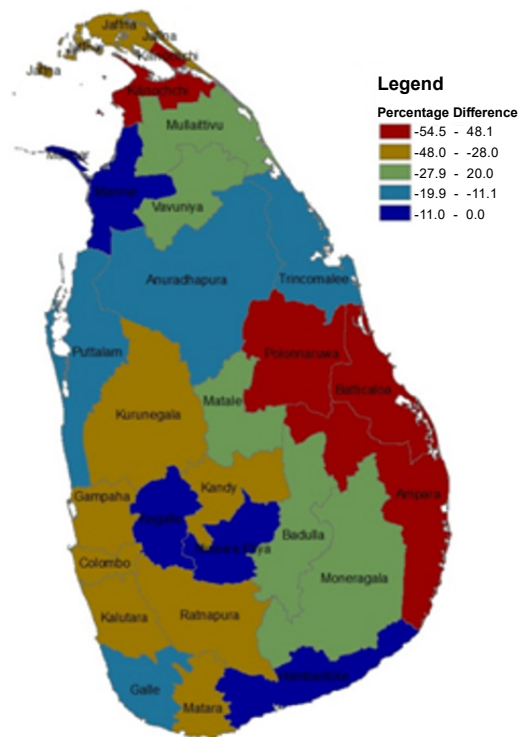
**Background:** Both Tuberculosis (TB) and COVID-19 are communicable diseases which mainly involve the respiratory system. Sri Lanka is a low prevalent country for TB. Currently, the world is facing catastrophic damages due to the biggest pandemic of the twentieth century. Common respiratory origin and interference with host

immunity, result in many clinical similarities between two diseases and the impact of COVID-19 on Tuberculosis healthcare is an area of great clinical significance.

**Methods:** Manual and electronic extraction of data from January- July of respective years - 2019 and 2020 received from District Chest Clinics were compared using Microsoft Excel and mapped and compared by using ArcGIS 10.7.1 software.

**Results:** During the first quarter(Q1) (January – March ) in the year 2019 and 2020 , total number of 2153 and 2043 TB cases were reported in Sri Lanka, respectively. A 5.1% decline in total number of TB cases in the year 2020 was reported in comparison to previous year .A decline in number of TB cases were observed in 15 out of 26 districts.

During the second quarter (April – July)(Q2) in the year 2019 and 2020 , total number of 2030 and 1446 cases were reported in Sri Lanka, respectively. A 28.8% decline in total number of TB cases in 2020 in comparison to previous year was reported. A decline in total number of TB cases in 25 out of 26 districts was reported in Q1-2020. Districts in the eastern part of Sri Lanka, including Batticaloa and Ampara and Polonnaruwa reported nearly a fifty percent decrease in total number of TB cases. Western Province including Colombo, Kalutara and Gampaha districts reported a decrease in one fourth of TB cases in comparison to the Q2 in 2019.



[Figure. Tuberculosis case finding comparison 2nd quarter 2019 & 2020, Sri Lanka]

**Conclusions:** The effect of COVID-19 pandemic on economy and health care services has a negative impact on TB case detection, treatment and follow up.

## LATE BREAKER PRESENTATIONS FRIDAY 23 OCTOBER 2020

### OA-30 The HIV-TB and diabetes late-breaker session

#### LB-1903-23 Diagnostic accuracy of a novel point-of-care urine lipoarabinomannan assay for the detection of tuberculosis among adult outpatients in Zambia: a prospective cross-sectional study

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**Background:** A novel, rapid, point-of-care urine-based lipoarabinomannan assay (Fujifilm SILVAMP TB-LAM, "FujiLAM") has previously demonstrated significantly improved sensitivity for tuberculosis (TB) compared to the commercially-available Determine TB-LAM assay using bio-banked specimens. However, to-date FujiLAM has not been prospectively evaluated. Therefore, we determined the diagnostic accuracy of FujiLAM among HIV-positive and HIV-negative outpatients with presumptive TB in Zambia.

**Methods:** Adults  $\geq 18$  years old presenting to two outpatient public health facilities in Lusaka, Zambia, without a current active TB diagnosis and with a positive WHO symptom screen were included. All patients submitted sputa samples for smear-microscopy, Xpert Ultra and Mycobacterial culture and urine samples for the FujiLAM assay. CD4 testing was not routinely performed. Microbiologically-confirmed TB was defined by the detection of Mycobacterium tuberculosis in sputum using either culture or Xpert Ultra and this was used as the reference standard to assess the diagnostic accuracy of FujiLAM.

**Results:** 153 adults with paired sputum microbiologic tests and urine FujiLAM results were included. The median age was 37 (IQR: 29-43), 58.8% (n=90) were male, and 45.8% (n=70/153) were HIV-positive. Overall, 38/153 patients had microbiologically-confirmed pulmonary TB (prevalence, 24.8%, 95% CI 18.2-32.5). The overall sensitivity and specificity of FujiLAM was 71.1% (n=27/38; 95% CI: 54.1-84.6) and 93.0% (n=107/115; 95% CI: 86.9-96.9), respectively. The sensitivity among

HIV-positive patients was 66.7% (n=10/15) compared to 71.4% (n=15/21) among HIV-negative patients. The sensitivity of FujiLAM in patients with smear-positive, confirmed pulmonary TB was 86.7% (n=13/15) compared to 60.9% (n=14/23) among patients with smear-negative, confirmed pulmonary TB.

**Conclusions:** FujiLAM demonstrated high sensitivity for the detection of TB among both HIV-positive and HIV-negative adults and also demonstrated high specificity despite the lack of systematic extra-pulmonary sampling to inform a comprehensive microbiological reference standard. While larger prospective studies are required, these results suggest that FujiLAM could significantly improve point-of-care TB diagnosis in resource-limited settings.

#### LB-1930-23 Glycemic trajectories after tuberculosis diagnosis and treatment outcomes of new tuberculosis patients: a prospective cohort study in Eastern China

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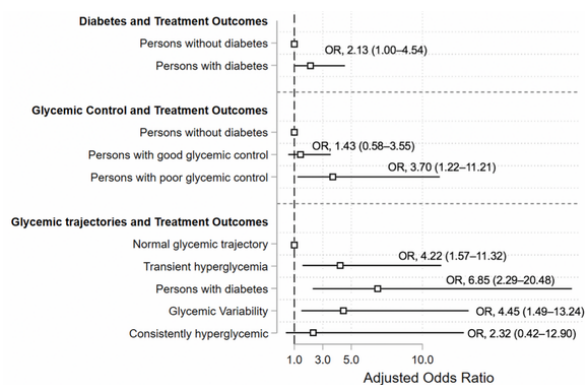
**Background:** Newly diagnosed tuberculosis patients often have abnormal glycemic measurements which may occur through diabetes or glycemic instability. The impact of differing glycemic trajectories during tuberculosis treatment on subsequent treatment outcomes is unknown.

**Methods:** New tuberculosis patients with at least three fasting plasma glucose (FPG) tests at tuberculosis diagnosis and during the 3rd and 6th month of treatment were included. Patients were also given an additional FPG test at two and four months post-treatment. Distinct glycemic trajectories from tuberculosis diagnosis to post-treatment were categorized. We assessed the relationship between each glycemic trajectory and subsequent tuberculosis treatment outcomes and examined potential modifiers of this relationship.

**Results:** Of 500 newly diagnosed tuberculosis patients, several distinct glycemic trajectories from tuberculosis diagnosis to post-treatment were found including diabetes, consistently normal glycemic testing, transient hyperglycemia, erratic glycemic variability, and consistently hyperglycemic but without diabetes. Compared to participants with consistently normal glycemic trajectories, patients were at much higher risk of poor treatment



outcomes if they had transient hyperglycemia (Adjusted Odds Ratio [AOR], 4.0; 95% Confidence Interval [CI], 1.5–10.8,  $P=0.006$ ) or erratic glycaemic variability (AOR, 5.9; 95% CI, 2.9–17.8,  $P=0.001$ ).



[Figure. Multivariable logistic regression analysis of glycaemic status and trajectories with tuberculosis treatment outcomes]

Almost 50% of all patients with poor tuberculosis treatment outcomes were among patients with either transient hyperglycemia or glycaemic variability. Patients living with diabetes also had high risk of poor treatment outcomes (AOR, 7.06; 95% CI, 2.3–21.3,  $P=0.001$ ), and this was modified by glycaemic control.

**Conclusions:** Our findings suggest that newly diagnosed tuberculosis patients with transient hyperglycemia or erratic glycaemic instability are at high-risk of treatment failure and death. Glycaemic kinetics, regardless of diabetes status, may be an important marker for patient response to tuberculosis treatment.

### LB-2044-23 Prevalence of diabetes mellitus amongst patients with tuberculosis in low- and middle-income countries: a systematic review of 39 cross-sectional studies

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**Background:** Diabetes mellitus (DM) and tuberculosis (TB) are both diseases of global proportions. They are among the top ten global causes of death and affect low- and middle-income countries (LMIC) disproportionately. But there is also a known bidirectional relationship between the two. Patients with DM have an increased risk for TB, worse TB treatment outcomes and increased risk of relapse and death. TB infection can also temporarily induce hyperglycaemia, leading to impaired glucose tolerance and TB treatment can derange glycaemic control. LMIC are often ill-equipped to tackle this “double burden” of both communicable and noncommunicable diseases. Understanding the prevalence of DM amongst patients with TB in LMIC and the percentage of those

newly diagnosed with DM as a result of screening would help understand if screening this patient population was worthwhile or if dual management of TB and DM was feasible.

**Methods:** A systematic review was conducted of cross-sectional studies that screened patients with TB for DM in LMIC, using the EMBASE and MEDLINE. The main outcome was the prevalence of DM detected through screening patients with TB and the percentage of patients newly diagnosed with DM.

**Results:** Thirty-nine studies met the inclusion criteria and were set in a TB clinic, health centre or a hospital. The average prevalence of DM amongst screened patients was 15.05%, ranging from 1% to 44%. The percentage prevalence of diabetes among the previously “non-diabetic” TB population ranged from 0.63% to 27.12%.

**Conclusions:** Undiagnosed DM prevalence amongst patients with TB is wide ranging and high prevalence rates tend to occur where the general population prevalence of DM is also high. Further research is required to understand what an optimal screening programme would be. This should be given high priority to improve health outcomes for patients with TB-DM comorbidity.

### LB-2071-23 Exploring barriers and facilitators of diabetes mellitus management within the Philippines tuberculosis programme: a mixed-methods patient-centered health systems study

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**Background:** The Philippines has a high burden of diabetes mellitus (DM) among people with tuberculosis (TB). This study aims to understand barriers and facilitators to DM service delivery within TB-DOTS clinics that impact on individual-level DM management.

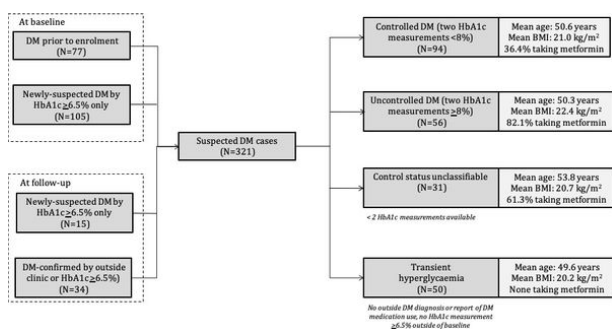
**Methods:** This sequential, explanatory mixed-methods study focuses on patients with DM in an ongoing cohort (N=813) of patients newly enrolling in TB treatment in 15 public TB-DOTS clinics in the Philippines (St-ATT



Cohort ISRCTN16347615). Data capturing DM and TB management were collected at baseline and monthly/tri-monthly. Data were analysed using Chi<sup>2</sup> tests to identify predictors of high hyperglycaemia ( $\geq 2$  glycated haemoglobin [HbA1c] measurements  $\geq 8\%$ ). Fifteen DM-TB patients were purposefully selected for semi-structured interview to explore quantitative findings. Nine structured facility observations and semi-structured interviews of three TB-DOTS providers describe DM service delivery context.

**Results:** At baseline, 77 patients reported previous DM diagnosis and 105 without previous DM diagnosis were hyperglycaemic (HbA1c $\geq 6.5\%$ ). At follow-up, 49 additional patients were identified as diabetic by report of external diagnosis, DM medication use, or HbA1c $\geq 6.5\%$ . Fifty suspected DM cases were dropped – presumed transiently hyperglycaemic (absence of external DM diagnosis, DM medication use, or follow-up HbA1c $\geq 6.5\%$ ).

Compared to patients with mild hyperglycemia (N=94), patients with high hyperglycemia (N=56) were demographically similar, but more likely to have DM prior to TB diagnosis (OR 7.11, 95% CI[3.38-14.94]), have a new case of TB (OR 2.30, 95% CI[1.12-4.72]), report numbness in limbs (OR 2.20, 95% CI[1.02-4.75] and use metformin (OR 7.09, 95% CI[3.19-17.76]). Qualitative findings indicate patients rely on TB-DOTS clinics for DM medications and MDR-TB patients divert special programme allowances to afford DM medication/supplies.



[Figure.]

**Conclusions:** We found that TB-DOTS clinics can provide a route to identify a substantial number of undiagnosed DM cases, and serve as a point of DM service delivery for patients undergoing TB treatment. Further observations will be conducted to explore in-depth DM service delivery context.

## LATE BREAKER PRESENTATIONS SATURDAY 24 OCTOBER 2020

### OA-39 The Union/CDC late-breaker session on TB

#### LB-2112-24 Diagnostic accuracy, clinical impact and antimicrobial resistance consequences of using trial-of-antibiotics for tuberculosis diagnosis: a randomised controlled trial in Malawi (ACT-TB study)

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**Background:** Tuberculosis (TB) diagnostic algorithms often include ‘trial-of-antibiotics’— empirical antibiotics for mycobacteriology-negative individuals to treat infectious causes other than tuberculosis, as a ‘rule-out’ diagnostic test for tuberculosis. We investigated the effect of trial-of-antibiotics among adults being investigated for TB on diagnostic accuracy, clinical outcomes, and antimicrobial resistance (AMR).

**Methods:** We randomised (1:1:1) Malawian adults (≥18 years) attending primary care for illness ≥2 weeks including cough not previously treated with antibiotics to receive: azithromycin (500mg once daily, 3 days), amoxicillin (1g three times/day, 5 days), or standard-of-care (SOC, no immediate antibiotic). Sputum taken at enrolment and day 8 was tested using mycobacteriology (microscopy, Xpert MTB/RIF, and TB culture). Nasopharyngeal swabs at enrolment and day 29 were cultured onto blood agar. Primary outcomes were specificity, defined as proportion reporting symptom improvement on audio computer-assisted self-interview at day 8 among those with negative mycobacteriology, and proportion

with composite day 29 endpoint of death, hospitalisation or missed tuberculosis diagnosis (clinical impact). The secondary outcome was the proportion with newly resistant nasopharyngeal *Streptococcus pneumoniae* on day 29. (NCT03545373).

**Results:** Between 02/2019-03/2020, we screened 2452 adults with cough and randomised 1583 (40% male, median age 32 years, 11.9% HIV-positive) to SOC (530), azithromycin (527), or amoxicillin (526). Overall 3.79% (60/1583) had positive mycobacteriology by day 8. Compared to SOC (79.1%), trial-of-antibiotics improved specificity of TB diagnosis: azithromycin vs. SOC (difference +7.40% [3.6%-11.2%]); amoxicillin vs. SOC (difference +6.70% [2.8%-10.6%]). Proportions with day 29 poor clinical outcomes (SOC 1.13%) or new AMR (SOC 5.28%) were similar (Table) including when antibiotic arms were combined.

Study arm (# randomised)	Standard of care (530)	Azithromycin (527)	Amoxicillin (526)	Amoxicillin or azithromycin (1053)				
Primary outcomes:								
Specificity: reported symptom improvement on day 8 among mycobacteriology negative (n/N*, %)	310/392	79.1	339/382	88.7	346/387	89.4	685/769	89.1
Specificity difference (95%CI), p-value	Ref	7.40% (3.57, 11.24)	<0.001	6.70% (2.82, 10.57)	0.001	7.05% (3.51, 10.58)	<0.001	
Composite endpoint of missed TB, hospitalisation and death by day 29 n/N, %	6/530	1.13	8/527	1.52	6/526	1.14	14/1053	1.33
Composite endpoint of missed TB, Hospitalisation and Death, (Risk difference [95%CI]), p-value	Ref	0.39% (-0.99, 1.76)	0.58	0.01% (-1.27, 1.29)	0.99	0.20% (-0.94, 1.33)	0.73	
Secondary outcome:								
Antimicrobial resistance positive at day 29 n/N, %	28/530	5.28	41/527	7.78	27/526	5.13	68/1053	6.46
Antimicrobial resistance positive at day 29 (Risk Difference [95%CI]), p-value	Ref	2.53% (-0.45, 5.51)	0.10	-0.17% (-2.86, 2.53)	0.90	1.18% (-1.24, 3.60)	0.34	

\*primary outcome denominator for specificity limited to mycobacteriology-negative participants  
CI = Confidence Interval. Ref=reference arm

[Table.]

**Conclusions:** Immediate trial-of-antibiotic during TB diagnosis investigations resulted in modestly increased but still suboptimal specificity, with no impact on early clinical outcomes or AMR generation. National programs can consider omitting routine trial-of-antibiotics from diagnostic algorithms, but more effective strategies to minimise unnecessary TB treatment are needed.

## LB-2087-24 Xpert performance evaluation for linkage to tuberculosis care (XPEL TB): a cluster-randomized trial

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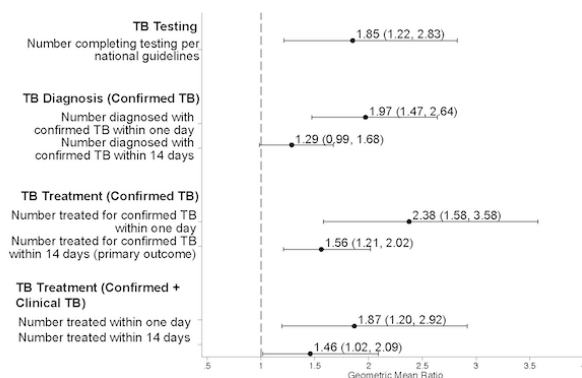
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**Background:** Prompt diagnosis and treatment of tuberculosis (TB) is critical to elimination. The XPEL TB trial assessed whether a streamlined diagnostic strategy centered around onsite Xpert MTB/RIF Ultra testing could increase TB diagnosis and treatment initiation.

**Methods:** We conducted an ultra-pragmatic cluster-randomized trial at 20 health centers (clusters) in Uganda. Restricted and stratified randomization was used to assign clusters, in a 1:1 ratio, to routine care (onsite smear microscopy and referral-based Xpert testing) or to the XPEL TB intervention including: 1) onsite Xpert Ultra testing using GeneXpert Edge; 2) guided restructuring of clinic workflow to facilitate same-day TB diagnosis and treatment; and 3) monthly feedback of TB evaluation-related quality metrics. Under a waiver of informed consent, we extracted routine TB register data to assess outcomes of all adults evaluated for pulmonary TB between October 2018-March 2020. The primary outcome – the number of adults diagnosed and treated for TB within 14 days – was analyzed using negative binomial regression, adjusting for pre-trial level of 14-day TB diagnosis and treatment.

**Results:** Of 10,691 eligible adults (intervention: 5,571; control: 5,120), 60% were female, 39% were HIV-positive, and median age was 40 years. The intervention strategy increased the number of patients diagnosed and treated for TB within 14 days (340 vs 218, geometric mean ratio [GMR] 1.56, 95% CI 1.21-2.02). In addition, more patients completed TB testing per national guidelines (GMR 1.85, 95% CI 1.22-2.83), were diagnosed

with microbiologically-confirmed TB on the same-day (GMR 1.97, 95% CI 1.47-2.64), and were treated for microbiologically-confirmed TB on the same-day (GMR 2.38, 95% CI 1.58-3.58).



[Figure: Forest plots of relative difference in TB diagnosis and treatment outcomes]

**Conclusions:** Onsite Xpert testing and implementation supports (clinic workflow restructuring and performance feedback) substantially increased 14-day TB diagnosis and treatment, as well as quality metrics at each step of the TB diagnostic evaluation care cascade.

## LB-2110-24 Comparable diagnostic performance of the T-SPOT®.TB test, using manual density gradient cell isolation versus automated positive selection with the T-Cell Select™ Kit

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**Background:** Improving diagnosis of latent TB infection (LTBI) is critical to achieve WHO END-TB targets. Increasing automation and extending time between blood collection and processing would broaden availability of the T-SPOT®.TB test, an interferon gamma release assay (IGRA), especially in settings with limited laboratory capacity.

We aimed to compare the T-SPOT.TB test using peripheral blood mononuclear cells (PBMCs) isolated via manual density gradient separation (reference) performed between 0-8 hours after blood collection, versus auto-

mated positive selection with magnetic bead isolation with the T-Cell *Select*<sup>TM</sup> Kit performed between 0-55 hours post collection.

**Methods:** Subjects were enrolled from four study sites with different prevalence rates of TB: Low (Mostly TB naïve; Site 1-Massachusetts and 2-Ohio), intermediate (mostly LTBI and high risk exposures; Site 3-Texas), and high (mostly participants with active TB disease; Site 4-South Africa). Demographic and clinical information was obtained and 20mL of blood was collected and divided into 4 samples processed at different time points. The T-SPOT.TB test was processed at 1-4 and 5-8 hours post venepuncture using the reference method and at 0-8, 18-32, 39-46 and 48-55 hours post venepuncture using the automated method with the T-Cell *Select* Kit.

**Results:** In total, 620 subjects were enrolled (Table 1). Ages ranged from 18-85 years, 41% male, 7% HIV-positive; 14% with LTBI and 15% with active TB disease. Each subject had four specimens processed at different time points, comprising 11889 specimens in total. Overall agreement between both methods was 96.8% [CI 95.9-97.6], with 95.8% [CI 93.5-97.5] positive and 97.1% negative agreements [CI 96.1-97.9].

	Combined N=620	Healthy Control		LTBI/ TB Exposures		TB Disease
		Site 1 (n=80)	Site 2 (n=346)	Site 3 (n=43)	Site 4 (n=151)	
Mean age (yrs) (SD)	40 (26-54.4)	33.8 (10.5)	42.9 (15.5)	38.7 (12.8)	38.6 (12.8)	
Age range (yrs)	18-95	18-61	18-85	19-66	18-73	
Male (%)	254 (41%)	36 (45%)	113 (33%)	13 (30%)	92 (61%)	
HIV Positive (%)	42 (7%)	2 (<1%)	1 (<1%)	0	39 (25%)	
BCG vaccination (%)	317 (51%)	16 (20%)	173 (50%)	37 (86%)	91 (60%)	
Latent TB Infection	87 (14%)	0	0	36 (84%)	51 (34%)	
Active TB Disease	90 (15%)	0	0	1 (2%)	89 (59%)	
Overall agreement [95%CI]	96.8% (1829/1889) [95.9-97.6]	98.0% (249/254) [95.5-99.4]	98.2% (1090/1110) [97.2-98.9]	89.3% (125/140) [82.9-93.9]	94.8% (365/385) [92.1-96.8]	

[Table 1. Demographic, clinical diagnosis, and Test Agreement]

**Conclusions:** There was a good overall concordance between the automated and manual T-SPOT.TB test processing methods. The T-SPOT.TB test can be processed using automated positive selection with magnetic bead isolation with T-Cell *Select* to decrease technician time without compromise for blood collection and processing times ranging from 0 to 55 hours.

## LB-2070-24 Deep learning algorithm classifies active TB, normal, and other abnormal chest X-rays with high accuracy on large scale dataset

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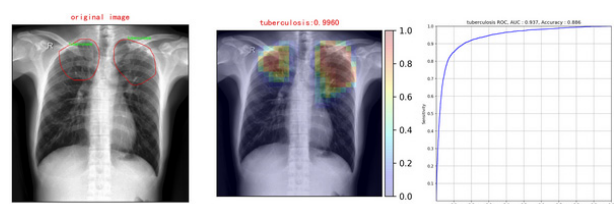
J. Chen,<sup>6</sup> W. Li,<sup>6</sup> K. Zhou,<sup>7</sup> J. He,<sup>7</sup> <sup>1</sup>JF Healthcare, Marketing, Nanchang, China, <sup>2</sup>Chinese Anti-Tuberculosis Association, Secretary Office, Beijing, China, <sup>3</sup>Chinese Academy of Medical Sciences & Peking Union Medical College, Institute of Pathogen Biology, Beijing, China, <sup>4</sup>China CDC, National Center for TB Control and Prevention, Beijing, China, <sup>5</sup>JF Healthcare, R&D, Nanchang, China, <sup>6</sup>JF Healthcare, Medical Department, Nanchang, China, <sup>7</sup>Nanjing Drum Tower Hospital, Radiology, Nanjing, China. e-mail: yuan.li@jfhealthcare.com

**Background:** Chest X-ray (CXR) exam is an important tool for TB triage, diagnosis, and screening. In this study, we aim to develop and evaluate CXR AI algorithm for TB screening programs to address radiologist shortage in high TB burden areas.

**Methods:** From 2018.4-2019.11, 22469 CXRs were collected to a TB research platform from 9 institutes of 6 provinces. A quality control check excluded 550 CXRs such as “not a posterior-anterior view”. Of the remaining, 4320 CXRs with the tag of “clinically diagnosed TB” (patients without a positive bacteriological confirmation but CXR and other test results consistent with TB) were used for training together with 98282 normal and 53197 other abnormal CXRs collected from a telemedicine network from hundreds of township hospitals in more than 10 provinces during 2018.1-2019.10. Each “TB image” was annotated by one of three board-certified radiologists to localize TB lesions through bounding boxes or masks.

The full training dataset was randomly split into 90% for training and 10% for validation. A ResNet-34 backbone CNN with a customized mask layer was trained to recognize TB. The remaining 17599 images from the TB big data platform, of which 5260 bacterially diagnosed TB, 6907 normal and 2094 other abnormal CXRs, formed the test dataset (3338 inactive TB CXR were not included).

**Results:** In the above test dataset, the AI algorithm achieved 0.94 AUC with 0.91 sensitivity and 0.81 specificity at the cutoff value of 0.20 for the TB probability score. Heatmaps were generated to locate the lesion on the image.



[Figure.]

**Conclusions:** The AI algorithm can classify active TB from normal and other abnormal CXR with high accuracy. It can be applied in TB screening programs where large amount of population are evaluated in a short period of time with limited radiologists.

### LB-2127-24 Tool to assess willingness to prescribe tuberculosis preventative therapy among healthcare workers in rural South Africa

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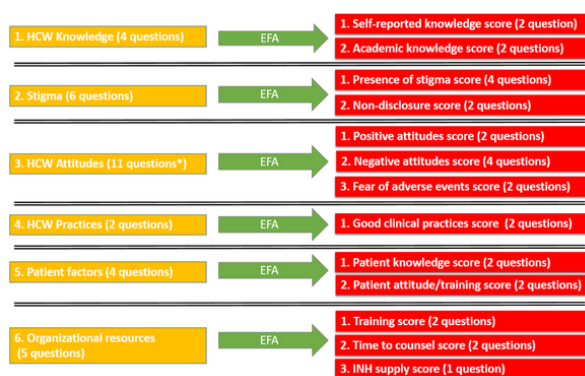
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**Background:** Despite the extensive rollout of tuberculosis preventative therapy (TPT) in South Africa to reduce the incidence of tuberculosis (TB) among people living with HIV, TPT implementation has been slow. We aimed to derive a tool to assess healthcare worker (HCW) willingness to prescribe TPT in rural South Africa.

**Methods:** An anonymous, cross-sectional survey was administered Nov-Dec 2019 to HCWs at a government district hospital and 14 primary care clinics in rural KwaZulu Natal, South Africa to obtain self-reported data on knowledge, attitudes, practices, and beliefs regarding isoniazid preventive therapy (IPT), the current TPT regimen. A response of “Every patient” to the pre-determined survey question “With how many of your patients that are HIV+ do you prescribe IPT to?” was used to determine willingness to prescribe the currently available TPT.

**Results:** The survey instrument was composed of 32 items in six categories (# of survey questions): HCW knowledge (4), stigma (6), HCW attitudes (11), HCW practices (2), patient factors (4), and organizational resources (5). Each item was transformed into a bivariate variable, and each category was subjected to exploratory factor analysis (EFA) using principal axis factoring and orthogonal varimax rotation with Kaiser Normalization. KMO's and Bartlett's test were used to determine if EFA was appropriate. Factors extracted had eigenvalues >1 and communalities >0.50.

The number of factors identified within each category are shown in **Figure 1**. Multivariable binary logistic regression was used to identify 2 factors associated with HCW willingness to prescribe TPT including absence of IPT stigma (aOR 3.31 95% CI 1.14-9.64, p=0.03) and patient willingness to disclose (aOR 3.30 95% CI 1.04-10.42; p=0.04).



[Figure 1. Flow chart of factor reduction of survey questions to thematic factors]

**Conclusions:** A tool to assess HCW willingness to prescribe was derived using exploratory factor analysis and regression analyses. With validation, this instrument will be valuable to identify how best to support HCWs to implement TPT.

### LB-2056-24 Shorter treatment for minimal tuberculosis in children: main findings from the SHINE trial

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**Background:** Children with non-severe tuberculosis (TB), represent 60-70% of all paediatric TB cases. These children generally have paucibacillary disease and may benefit from shorter treatment duration.

**Methods:** SHINE was an open-label treatment shortening trial in children with minimal (non-severe and smear-negative), symptomatic drug-susceptible TB, in 3 African (Zambia, Uganda, South Africa) and 2 Indian sites. Children <16 years were randomised to 4- versus 6-month treatment using WHO-recommended paediatric fixed-dose formulations (8 weeks isoniazid/rifampicin/pyrazinamide +/- ethambutol, followed by either 8 or 16 weeks of isoniazid/rifampicin).

Primary efficacy outcome was the proportion of children with unfavourable outcome (treatment failure, on-treatment loss-to-follow-up, TB recurrence or death by 72 weeks). The study was powered on a key subgroup independently adjudicated to have TB at base-



line (assumed to be 80%); the non-inferiority margin was 6%. Primary safety outcome was grade  $\geq 3$  adverse events during treatment.

**Results:** 1204 children were enrolled between July 2016 and July 2018; median age 3.5 years (range 2 months-15 years), 52% male, 11% HIV-infected, 14% culture/GeneXpert-positive. Retention by 72 weeks and adherence to the allocated treatment were 95% and 94%, respectively. In the modified intent-to-treat population, 16(3%) children had unfavourable outcomes on 4-month versus 18(3%) on the 6-month arm: difference -0.3%, 95% CI unadjusted (-2.3, 1.6). Non-inferiority of 4-month treatment was consistent across intention-to-treat, per-protocol and in those adjudicated to have TB at baseline, and in pre-specified subgroup analyses (Figure). 95(8%) children experienced grade  $\geq 3$  adverse events during treatment, including 16 adverse reactions (11 hepatic), similar across arms.

**Conclusions:** 4-month was as good as 6-month treatment for drug-susceptible minimal TB in children, and this treatment duration should be considered to reduce the treatment burden on children, caregivers and health services. Program implementation requires clear messaging to identify children with minimal TB to allow for stratified approaches to paediatric TB treatment.

### LB-2046-24 Temporal non-adherence and TB treatment outcomes? 'O art of subtlety and secrecy!'

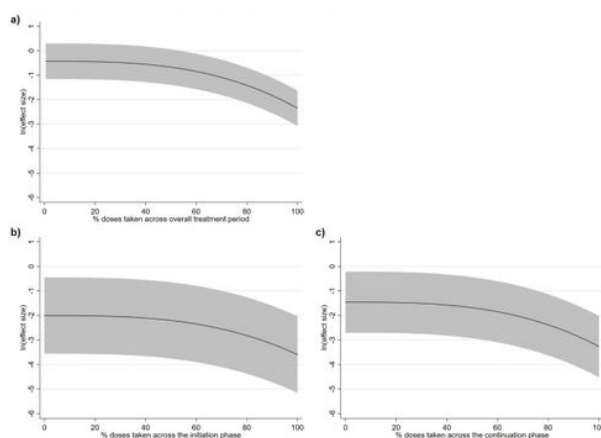
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**Background:** Low adherence to anti-tuberculosis treatment is associated with poor outcomes, development of secondary drug resistance, and transmission. All too frequently, adherence levels are reduced to binary categorisations (above 80/90% is 'good'), ignoring the temporal subtleties of adherence behaviours and the potential intricacies of the adherence-outcome relationship. We sought to determine this relationship in more detail, including the dynamics of adherence between the initiation and continuation phases.

**Methods:** Data from the RIFAQUIN, REMoxTB and Oflotub treatment-shortening trials for pulmonary drug-sensitive tuberculosis were analysed (3,918 individuals). Multivariable regression models were used to estimate the risk of an unfavourable outcome (poor treatment outcome or relapse), with a fixed effect for study site and country. Fractional polynomials were fitted to overall adherence, initiation phase adherence, and

continuation phase adherence within these models. A mediation analysis was conducted to examine what proportion of the impact of initiation phase adherence on unfavourable outcome was mediated through the adherence in the continuation phase.

**Results:** A cubic relationship was observed between adherence and the likelihood of a negative treatment outcome for overall treatment adherence, adherence during the initiation phase and adherence during the continuation phase (Figure). Converting this into relative risks and using 100% adherence as the baseline, the risk of a negative outcome was found to be 6.70 times higher (95% confidence interval 5.86-7.67) at 20% overall treatment adherence; 4.84 times higher (4.18-5.59) at 20% initiation phase adherence, and 6.04 times higher at 20% continuation phase adherence (5.33-6.83). Continuation phase adherence was found to mediate 24% of the marginal total effect between initiation phase adherence and an unfavourable outcome.



[Figure. Fractional polynomials of the relationship between non-adherence and treatment outcomes at different time points. Likelihood of a negative treatment outcome or relapse for different levels of non-adherence during the a) Overall treatment period, b) Initiation phase, c) Continuation phase. Fractional polynomials fitted in a model adjusted for age, sex, ethnicity, HIV status, smear status at baseline, cavitation at baseline, length of treatment, and location of data collection.]

**Conclusions:** The likelihood of a negative treatment outcome was strongly influenced by precise levels of non-adherence. Regimen and intervention design should take into account the important of adherence in different phases and the relationship between the two.



## TBSCIENCE2020 ORAL ABSTRACTS

### TBS1B Role of innate and adaptive immunity in TB and evaluation of immune correlates in pre-clinical and clinical studies: oral abstract presentations

#### TBS-OA-01 Inflammatory markers in the cerebrospinal fluid linked to mortality in tuberculous meningitis

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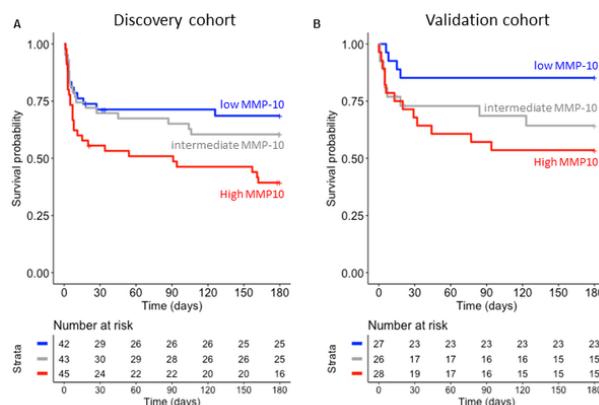
**Background:** Damaging and/or ineffective host responses contribute to the high mortality of tuberculous meningitis, but the underlying mechanisms remain largely unknown.

**Methods:** We measured 94 inflammation-related proteins using a multiplex immunoassay in cerebrospinal fluid (CSF) of 131 tuberculous meningitis patients and 43 control patients without meningitis from Hasan Sadikin Hospital in Bandung, Indonesia. A second group of 81 meningitis patients were studied as a validation cohort. In addition, genome-wide single nucleotide polymorphism typing was used to identify quantitative trait loci (QTLs) for CSF proteins analyzed in 209 of these patients, and these QTLs were used for survival analysis in an independent prospective cohort of 218 patients.

**Findings:** Overall, 70 of 94 proteins were detected in at least 75% of the CSF samples and were included in the analysis; 67 (96%) of these differed between tuberculous meningitis patients and control individuals (false discovery rate < 0.05), with 64 of them higher in patients. Among tuberculous meningitis patients, 5 proteins significantly predicted 180-day mortality, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase-10 (MMP-10, **Figure 1A**). The link between CSF VEGF concentrations and mortality could not be validated in a second set of patients, but CSF MMP-10 concentrations were also predictive of mortality in the validation cohort (**Figure 1B**). QTL-mapping identified 11 genetic loci that predicted CSF MMP-10 concen-

trations in tuberculous meningitis, and together, these genetic loci predicted survival in an independent set of patients.

**Interpretation:** High CSF concentrations of MMP-10 show a strong association with increased mortality of tuberculous meningitis, possibly because of its role in immunopathology. The genetic correlates for MMP-10 in tuberculous meningitis suggest a causal role in disease pathogenesis, and a possible benefit of targeting MMP with host-directed therapy to improve outcome of tuberculous meningitis.



[Figure 1. Cerebrospinal fluid MMP-10 concentrations predict survival in tuberculous meningitis. Kaplan-Meier graph with survival table for patients of the discovery (N = 130, A) and the validation cohort (N = 81, B) based on cerebrospinal fluid MMP-10 concentrations divided in tertiles]

#### TBS-OA-02 Vaccination with intravenous BCG protects SIV+ macaques from tuberculosis

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Tuberculosis (TB) is the most common infection in people living with HIV (PLHIV). Bacille Calmette-Guerin (BCG), a live attenuated *Mycobacterium bovis* strain given intradermally to infants, is the only licensed vaccine to prevent TB. However, BCG offers little protection from pulmonary TB in adults and safety concerns limit its use in PLHIV. Recently, intravenous (IV) BCG has been shown to provide striking protection from TB in rhesus macaques and was associated with a rapid and sustained increase in lung T cells. Given this dramatic success, we tested whether IV BCG could protect macaques with a pre-existing, chronic SIV infection using

our established model of SIV/Mtb coinfection in Mauritian cynomolgus macaques (MCM). MCM were intrarectally infected with SIVmac239 and 5 months later vaccinated with  $7 \times 10^7$  CFU BCG delivered IV.

Beginning 4 weeks later, vaccinated animals were treated with an 8-week regimen of isoniazid/rifampin/ethambutol (HRE) to prevent disseminated BCG. Four weeks after stopping antibiotics, animals were challenged with low-dose *Mycobacterium tuberculosis* (Mtb) Erdman strain via bronchoscope. Control animals consisted of SIV+ unvaccinated MCM and SIV-naïve, IV BCG-vaccinated MCM.

Even prior to HRE treatment, SIV+ MCM exhibited no signs of BCG disease. Flow cytometry of BAL revealed a rapid and sustained increase in airway T cells following BCG vaccination in both SIV+ and SIV- animals.  $^{18}\text{F}$ -FDG PET/CT imaging showed rapid TB progression in unvaccinated, SIV+ animals but complete absence of inflammation in 6 of 7 vaccinated SIV+ MCM.

Remarkably, necropsy 12 weeks after Mtb challenge showed the protected animals to be free of active TB and without culturable bacilli in their tissues. IV BCG is safe, immunogenic, and extraordinarily protective in SIV+ macaques.

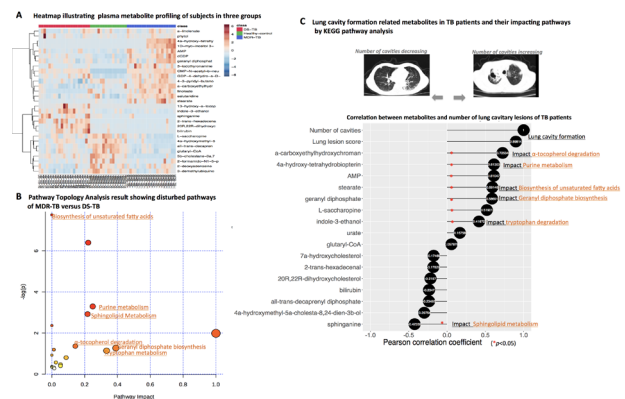
### TBS-OA-03 A pilot study on plasma metabolomic characterization of patients with MDR-TB

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**Background:** Metabolic dynamics can impact host immune response against *Mycobacterium tuberculosis* (TB). This pilot study aimed to determine whether patients developing multi-drug resistant tuberculosis (MDR-TB) had distinguished plasma metabolic profile and whether this profile was associated with drug resistance and immunopathology in MDR-TB, which is still a big challenge to control globally.

**Methods:** Plasma samples were collected from a cohort of healthy donors (HC group) and a cohort of TB patients before their treatment regimen beginning, including the MDR-TB group with previous DS-TB history (n=20) and the Drug-sensitive tuberculosis (DS-TB) group with no previous TB history (n=20). Plasma metabolite profiles were determined by liquid chromatography–quadrupole time-of-flight mass spectrometry and were analyzed by multivariate statistics. Pearson's correlation analysis was performed to assess relationships between the identified metabolites and clinical severity of TB patients. Disturbed metabolism pathways were identified using KEGG database and topology analysis.

**Results:** A total of 29 changed metabolites were identified with distinguished profiling among HC group, DS-TB group and MDR-TB group (Fig1 A). We illustrated possible disturbed metabolism pathways between MDR-TB and DS-TB patients by topology analysis (Fig1 B). A total of 9 metabolites was significantly correlated to the lung cavity numbers and lung lesion scores on chest CT in TB patients ( $p < 0.05$ ). A total of six pathways identified from the lung cavity related metabolites by KEGG analysis (Fig1 B,C) matched the six of eight significant impacted pathways between MDR-TB and DS-TB patients (Fig1 B,C). All these matched pathways had been previously linked to human macrophage functions.



[Figure 1.]

**Conclusions:** Our findings show distinguished plasma metabolite profiles in MDR-TB patients and lung cavity formation with innate immunity dysfunctions could potentially impact drug resistance dynamics during TB infection. Identifying the related metabolites and pathways would contribute to discovering potential treatment targets and future study of immunopathology and drug resistant mechanisms in MDR-TB patients.

## TBS-OA-04 A 22-gene transcriptomic model predicting individual therapy durations in multidrug-resistant tuberculosis

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**Background:** Emerging multidrug-resistant tuberculosis is a major global health challenge. The World Health Organization currently recommends a treatment duration of 9-18 months or more for patients with multidrug-resistant tuberculosis. We aimed to identify and validate a host-RNA signature to serve as a biomarker for individualized multidrug-resistant tuberculosis therapy duration.

**Methods:** Adult patients with pulmonary tuberculosis were prospectively enrolled into 5 independent cohorts in Germany and Romania. Clinical and microbiological data, and whole-blood for RNA transcriptomic analysis were collected at pre-defined timepoints throughout therapy. Treatment outcomes were ascertained one year after end-of-therapy. A whole-blood RNA therapy end model was developed in a multi-step process also involving a machine-learning algorithm to identify individual end-of-treatment timepoints.

**Findings:** Forty-nine patients with drug-susceptible tuberculosis and 30 patients with multidrug-resistant tuberculosis were recruited in the German identification cohorts (DS- and MDR-GIC), 32 patients with drug-susceptible tuberculosis and 28 patients with multidrug-resistant tuberculosis in the German validation cohorts (DS- and MDR-GVC), and 52 patients with multidrug-resistant tuberculosis in the Romanian validation cohort (MDR-RVC). A 22-gene RNA therapy end model that defined cure-associated end-of-therapy timepoints was derived from the DS- and MDR-GIC data. The model accurately predicted clinical outcomes within the independent DS-GVC patients (AUC=0.937 [95%CI:0.899-0.976]) and suggested that cure may be achieved with shorter treatment durations for MDR-GIC (mean reduction 167.7 days, 27.4%, p<0.001), MDR-GVC (mean reduction 177.1 days, 27.3%, p<0.001), and MDR-RVC (mean reduction of 115.8 days, 19.6%, p=0.198) tuberculosis patients.

**Interpretation:** A 22-gene RNA therapy end model yielded individual treatment durations for patients with multidrug-resistant tuberculosis. The therapy end model may enable individual anti-tuberculosis therapy durations in the future.

## TBS2B Bacterial metabolic activity and the host response in TB disease: oral abstract presentations

### TBS-OA-05 Transcriptomic profile of aerosolized *Mycobacterium tuberculosis* from patients during the early phase of drug-sensitive anti-tuberculosis treatment

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Experimental evidence shows that with minimal effective treatment, pulmonary tuberculosis (PTB) patient's ability to infect others is lost much before smear or culture conversion. Currently, not much is known about the mechanism of reduced infectiousness in the early stages of effective treatment.

We evaluated changes in transcriptional patterns of aerosolized tuberculosis bacilli on treatment initiation and compared with its treatment naïve profile. *Mycobacterium tuberculosis* (Mtb) global gene expression profile was analyzed via RNA sequencing in bioaerosols collected from six PTB patients pre-treatment and on days 1, 3, 5, 7 and 14 of treatment.

The principal component analysis showed separate clustering of expressed genes pre and post-treatment initiation, indicating that transcriptional changes are apparent immediately after treatment initiation (post-1-day) and are sustained even on day 14 of treatment.

Drug treated Mtb bacilli displayed downregulation of essential genes and genes encoding metabolic activities, DosR regulon, and efflux pumps. Also, genes associated with ESX system, chaperones, iron assimilation, and sulfur metabolism were downregulated indicating loss of pathogenicity and a diminished ability of infection and survival in new host cells. Similar alterations in Mtb gene expression were not seen in patients who received ineffective treatment.

The study provides the first view of the transcriptome of aerosolized Mtb - a more accurate correlate of transmission than surrogate sputum sample - during early treatment. The alterations in gene expression associated mainly with cell wall components and processes suggest that treatment leads to functional changes in the cell wall. The cell wall is the key contact point of the bacteria for interaction with host cells and changes in these components may explain the loss of infectiousness. The alterations of Mtb global gene expression during early treatment can be used to monitor response to the treatment regimen and develop biomarkers to predict treatment efficacy or loss of infectiousness.

### TBS-OA-06 Antigen-specific T cell activation distinguishes between recent and remote tuberculosis infection

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**Rationale:** Provision of preventive treatment to individuals with *Mycobacterium tuberculosis* infection is a key strategy to reduce the global tuberculosis burden. Tuberculosis risk is significantly higher after recent compared to remote infection.

**Objectives:** To define a blood-based biomarker, measured with a simple flow cytometry assay, that can stratify different stages of tuberculosis infection to infer risk of disease.

**Methods:** Adolescents were serially tested with QuantiFERON-TB Gold (QFT) to define recent (QFT conversion <6 months) and remote (persistent QFT+ for >1 year) infection. We defined the  $\Delta$ HLA-DR median fluorescence intensity (MFI) biomarker as the difference in HLA-DR expression between IFN- $\gamma$ +TNF+ *Mycobacterium tuberculosis*-specific and total CD3+ T cells. Biomarker performance was assessed by blinded prediction in untouched test cohorts with recent versus remote infection or tuberculosis disease, and unblinded analysis of asymptomatic adolescents with tuberculosis infection who remained healthy (non-progressors) or who progressed to microbiologically-confirmed disease (progressors).

**Results:** In the test cohorts, frequencies of *Mycobacterium tuberculosis*-specific T cells differentiated between QFT- (n=25) and QFT+ (n=47) individuals (area under the ROC curve and 95% confidence intervals: 0.94; 0.87-1.00).  $\Delta$ HLA-DR MFI significantly discriminated between recent (n=20) and remote (n=22) infection (0.91; 0.83-1.00); remote infection and newly diagnosed tuberculosis (n=19, 0.99; 0.96-1.00); and between tuberculosis progressors (n=22) and non-progressors (n=34, 0.75; 0.63-0.87).

**Conclusion:** The  $\Delta$ HLA-DR MFI biomarker can identify individuals with recent tuberculosis infection and those with disease progression, allowing targeted provision of preventive treatment to those at highest risk of tuberculosis.

### TBS-OA-07 Self-clearance of *Mycobacterium tuberculosis* infection: implications for lifetime risk and population at-risk of tuberculosis disease

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**Background:** It is widely assumed that individuals with *Mycobacterium tuberculosis* (*Mtb*) infection remain at lifelong risk of tuberculosis (TB) disease. However, there is substantial evidence that self-clearance of *Mtb* infection can occur, after which individuals can no longer progress to disease in the absence of reinfection. In this work we infer a curve of self-clearance by time since infection and explore its quantitative implications for TB epidemiology.

**Methods:** Data for self-clearance by time since infection were inferred using post-mortem and tuberculin skin test reversion studies. A TB cohort model allowing for self-clearance of *Mtb* infection was fitted in a Bayesian framework. We estimated how self-clearance changes the lifetime risk of TB disease and the population infected with *Mtb* in India, China and Japan in 2019.

**Results:** We estimated that 24.4% (17.8-32.6%, 95% uncertainty interval (UI)) of individuals self-clear within 10 years of infection, and 73.1% (64.6-81.7%) over a lifetime. The lifetime risk of TB disease amongst individuals retaining a viable infection was 17.0% (10.9-22.5%), compared to 12.6% (10.1-15.0%) assuming lifelong infection. The population at risk of TB disease in India, China and Japan was 35-80% (95% UI) smaller in the self-clearance scenario.

**Conclusions:** The population with a viable *Mtb* infection may be markedly smaller than generally assumed, with fewer individuals retaining an infection, yet each at greater risk of TB disease. The ability to identify these individuals could dramatically improve the targeting of preventive programmes and inform TB vaccine development, bringing TB elimination within reach of feasibility.

### TBS-OA-08 Cough-independent production of metabolically active *Mycobacterium tuberculosis* in bioaerosol

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**Rationale:** Symptoms of infectious respiratory illnesses are often assumed to drive transmission. Although *Mycobacterium tuberculosis* (*Mtb*) bioaerosols are essential for pulmonary tuberculosis (PTB) transmission, their production and release are poorly understood. Recent advances in capture and detection, enable quantitation of *Mtb* exhaled during specific respiratory manoeuvres. **Objective:** Is *Mtb* bacilli exhalation independent of cough?

**Methods:** A comparison of direct capture of nascent bioaerosol particles and indirect collection of aged particles was performed in 10-healthy subjects. Direct and indirect capture of exhaled metabolically active *Mtb* bacilli was compared in 38 PTB patients and directly captured metabolically active *Mtb* during cough and bronchiole-burst manoeuvres in 27 of the PTB patients.

**Measurements and main results:** Direct sampling of healthy subjects captured larger bioaerosol volumes with higher proportions of 2-5micron particles than indirect sampling. Indirect sampling identified metabolically active *Mtb* in 92.1% (35 of 38) of PTB patients during 60-minutes relaxed breathing and the median bacillary count was 7.5 (IQR: 3.25-19). Direct sampling for 10-minutes identified *Mtb* in 97.4% (37 of 38) of PTB patients with higher bacilli counts ( $p < 0.001$ ), median 24.5 (IQR:11.25-37.5). A short 5-minute sampling regimen of 10 coughs or 10 bronchiole-burst manoeuvres yielded a median of 11 (IQR: 4-17) and 11 (IQR: 7-17.5) *Mtb* bacilli, respectively ( $p = 0.53$ ).

**Conclusions:** Rapid collection of nascent bioaerosols combined with sensitive bacterial detection has diagnostic potential and may allow elucidation of asymptomatic transmission often inferred but not demonstrated. Peripheral lung bioaerosol released through deep exhalations alone contained metabolically active *Mtb* suggesting non-cough transmission is possible in PTB and other infectious pneumonic diseases.

## TBS3B Latest research in drug resistance detection, mechanism and treatments: oral abstract presentations

### TBS-OA-09 Association of delamanid concentrations with treatment outcomes or drug resistance among patients with MDR-TB

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**Background:** Delamanid is a newly available drug for treating multidrug-resistant tuberculosis (MDR TB), but there are limited data on the association between serum concentrations and clinical outcomes or drug resistance.

**Methods:** A prospective observational study enrolled delamanid-naïve patients with MDR TB in Georgia receiving a delamanid-based treatment regimen from July 2014 to October 2015. Whole genome sequencing of *M. tuberculosis* isolates was performed. Monthly sputum cultures, MIC testing for drugs other than delamanid, and one-time intensive pharmacokinetic testing (C<sub>max</sub>, C<sub>min</sub>, and AUC) were obtained. Outcomes were culture conversion, clinical outcomes, and development of genetic resistance to delamanid.

**Results:** Among 100 patients with MDR TB, 30 received a delamanid-based regimen. Most were male (67%) and median age was 38 years. The most common co-administered drugs included linezolid, clofazimine, and fluoroquinolones. Mutations associated with delamanid resistance (Rv3547 or Rv1173) were identified in baseline isolates from 5 patients (5%); none received a delamanid-based regimen. Among 30 patients who received delamanid; 23 (77%) achieved sputum culture conversion. Delamanid pharmacokinetic parameters were lower but not significantly different in those without culture conversion or who acquired drug resistance (Table). For those without culture conversion, median C<sub>max</sub> was 0.23 vs. 0.33 µg/mL (p=0.44), C<sub>min</sub> 0.16 vs 0.18 µg/mL (p=0.60), and AUC 2.52 vs. 2.86 µg/mL (p=0.60). Proportion attaining culture conversion (78.3 vs 66.7%, p=0.45) and days to culture conversion (median 78.5 vs 52.5, log-rank p=0.51) did not significantly differ between those with or without C<sub>max</sub> greater than 0.2 µg/mL. 10 patients (33%) acquired resistance to any drug during therapy.

**Conclusions:** Genetic mutations associated with delamanid resistance occurred at baseline in 5% of delamanid-naïve patients with MDR TB. While delamanid

pharmacokinetic parameters were not significantly associated with lack of culture conversion or acquired drug resistance, there was a trend towards lower serum concentrations in patients with these outcomes.

Measure (median, IQR)	Culture conversion (n=22)	No culture conversion (n=7)	p-value	Acquired drug resistance (n=10)	No acquired drug resistance (n=19)	p-value
C <sub>max</sub>	0.333 (0.246, 0.418)	0.228 (0.195, 0.485)	0.44	0.238 (0.195, 0.324)	0.342 (0.246, 0.485)	0.09
C <sub>min</sub>	0.183 (0.123, 0.249)	0.162 (0.067, 0.273)	0.60	0.158 (0.067, 0.203)	0.187 (0.123, 0.317)	0.15
AUC	2.858 (2.157, 3.782)	2.515 (1.436, 5.101)	0.60	2.507 (1.436, 3.138)	3.045 (2.157, 5.199)	0.12

[Table. Pharmacokinetic measurements and outcomes for 100 patients with MDR-TB treated with delamanid.]

### TBS-OA-10 High frequency of bedaquiline resistance in programmatically treated drug-resistant TB patients with sustained culture-positivity in Cape Town, South Africa

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New tuberculosis (TB) drugs, like bedaquiline, are a significant advance in TB care and improved outcomes. Consequently, bedaquiline is undergoing wide roll-out, however this is largely in the absence of programmatic drug susceptibility testing (DST). We lack information on how susceptibility changes during treatment in patients on bedaquiline-containing regimens, especially in those who have a delayed treatment response (sustained culture-positivity), complex treatment histories, and in a programmatic rather than clinical trial environment. Serial isolates from 51 patients with drug resistant (DR-) TB, culture-positive after ≥ 4 months of a bedaquiline-containing regimen, were collected. Bedaquiline phenotypic DST in MGIT 960 (1µg/ml), targeted deep sequencing (*Rv0678*, *atpE* and *pepQ*) and whole genome sequencing was done on pre-bedaquiline initiation and post-four-month isolates. 24/51 (47%) patients with sustained culture-positivity were phenotypically and genotypically resistant. Excluding one patient with an unknown treatment history, prior clofazimine exposure was associated with bedaquiline-resistance [21/24 (88%) resistant cases had prior clofazimine vs. 12/26 (46%) susceptibles; p=0.002]. Diverse combinations of single nucleotide polymorphisms (SNPs) and indels were seen in bedaquiline resistance-associated genes (*Rv0678*, *atpE*) and the *Rv0678* promoter region.



Examples of newly described variants are *Rv0678* -8 T/G promoter and *atpE* 223 C/T, both in phenotypically resistant isolates. *Rv0678* resistant associated variants (RAVs) were not in specific hotspots and sometimes occurred concurrently with RAVs in *atpE*. 47% of programmatically treated DR-TB patients with sustained culture-positivity were bedaquiline-resistant and 39% of patients had strains that acquired resistance. Prior clofazimine was associated with bedaquiline-resistance. The genotypic resistance-associated diversity observed poses challenges for molecular test development.

This study highlights the existence of a potentially infectious pool of bedaquiline-resistant patients under programmatic conditions and the danger of starting patients with complex histories on a novel drug without routinely available DST.

### **TBS-OA-11 *ncRv0842c*, a smallRNA regulating the efflux pump *Rv0842* involved in rifampicin tolerance in *M. tuberculosis***

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Regulatory pathways mediated by smallRNAs (sRNAs) in *Mycobacterium tuberculosis* (MTB) are still poorly understood. We identified the sRNA *ncRv0842c* cis-encoded to the *Rv0842* gene, an efflux pump involved in rifampicin resistance (RIF-R) in MTB. The aim of our study is to characterize the role of *ncRv0842c* during RIF challenge.

We performed expression analysis of the sRNA by qRT-PCR in different RIF-R and RIF-S isolates representative of ancient (L5) and modern (L2, L4) MTB lineages (reference: H37Rv strain). Expression analysis of the sRNA and its target during RIF challenge (sub-inhibitory concentrations 25-50-90% MIC) was performed in L5 and in H37Rv at different time-points (0.5-6-24 h). Overexpression of *ncRv0842c* was achieved by the use of a pMV261 plasmid. RIF MIC was determined by microplate Alamar Blue assay (MABA).

Basal expression analysis showed a strong down-regulation of the sRNA *ncRv0842* in L5 compared to modern lineages (x0.03125, p-val <0.05). During RIF challenge the efflux pump was up-regulated (x3, p-val <0.05), whereas the sRNA was down-regulated (x0.25, p-val <0.05) in H37Rv. In L5 the sRNA expression was consistently not affected by RIF stress, whereas the efflux pump did not show induction. WGS analysis revealed a silent mutation in *Rv0842* (L45L) specific for the ancient lineages (L1, L5, L6) abrogating the -10 promoter region of the cis-encoded sRNA. Preliminary data on the *ncRv0842c* overexpressing mutant in MTB H37Rv background showed a 1 dilution reduction of the MIC for RIF.

*ncRv0842c* is involved in the regulation of *Rv0842* during RIF challenge, thus contributing to the fine-tuning of the efflux pump in MTB. The silent mutation mapping in the *Rv0842* gene of ancient lineages was found to negatively affect the expression of *ncRv0842c*. Our results open to a better understanding of the role of silent mutations in MTB stress response and further highlight genotype-specific features in MTB.

### **TBS-OA-12 Genomic sequence characteristics and the empirical accuracy of short-read sequencing in *Mycobacterium tuberculosis***

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Short-read whole genome sequencing (WGS) is a vital tool for both clinical and basic research of *Mycobacterium tuberculosis* (Mtb). The presence of genomic variants is often inferred from the alignment of short sequencing reads to a reference genome. Genetic divergence from the reference genome and repetitive sequence elements reduce the accuracy of variant calling from short-read alignment but the loss in recall and specificity has not been adequately characterized. For Mtb, researchers often exclude ~10% of the genome believed to be repetitive and prone to false positive variant calls.

Here, we systematically studied reference genomic characteristics, including sequence uniqueness, GC content as well as query divergence from the reference as predictors of variant calling accuracy in 27 Mtb isolates sequenced by both Illumina short-read and PacBio long-read technology. Variant calling errors are concentrated in regions with low sequence uniqueness.

Critically, we observe that ~58% of the routinely excluded Mtb genome can be confidently genotyped by short read sequencing. Guided by these results, we provide improved variant filtering of the Mtb genome that improves SNP variant recall by ~10% with little to no loss in precision.

Our improved approach to variant calling has broad implications for the use of WGS in the study of Mtb biology, inference of transmission in public health surveillance systems, and more generally for WGS applications in other organisms.

## **TBS4B Innovations in TB therapeutics: oral abstract presentations**

### **TBS-OA-13 An empirical modeling approach for regimen development: How to build a winning team**

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Accelerated tuberculosis drug discovery has led to several promising drug candidates that require more efficient and predictive strategies for selecting regimens to progress to clinical trials. Evaluating every possible drug-dose combination experiment in long-term in vivo efficacy models such as the relapsing mouse model is impractical and the potential discordance between initial bactericidal activity and long-term sterilizing activity can mean ranking by CFU decrease will not translate to relapse-free cure. Using historical data from a relapsing mouse model of TB we developed mathematical models to predict relapse and rank regimens by their sterilization potential.

We pooled 28 BALB/c mouse datasets and included 17 regimens, 2860 relapse, and 1539 CFU observations in our final dataset. Potential predictors included inoculation size, incubation time, baseline lung CFU count, 28-day CFU decrease from baseline, duration of treatment, and 10 drugs of 5 classes. The probability of relapse was determined using logistic regression. A step-wise univariate and multivariate analysis provided a baseline model to standardize experimental conditions, followed by the addition of drugs to assess their sterilization contribution to regimens. We also applied machine learning approaches including neural networks, random forest, and decision tree analysis to compare methods.

The final model had a ROC AUC of 0.910 and showed that bacterial kill measured by CFU cannot predict relapse alone and sterilization is drug-dependent. The model could, therefore, rank the most sterilizing drugs within and between different classes and which drug combinations were more synergistic at preventing relapse. We could also rank regimens based on the shortest treatment duration needed to prevent relapse and further optimize an ideal duration for each regimen. Based on our models the diarylquinolines had the best sterilizing activity and the addition of an oxazolidinone provided the best backbone for shortening treatment duration. Additionally, all regimens benefit from the addition of pyrazinamide.

### TBS-OA-14 The role of respiratory microbiome in early bactericidal activity of anti-tuberculosis therapy and treatment outcome

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Tuberculosis (TB) treatment takes minimum of six months on a four-drug regimen. We sought to understand effect of anti-TB antibiotics on respiratory microbiome and how this relates to patient treatment outcome.

The microbiome of sputum samples from patients at baseline to 3 months of treatment with either standard regimen Isoniazid(H)-Rifampicin(R)-Pyrazinamide(Z)-Ethambutol(E) (HR<sub>600mg</sub>ZE) or high-dose rifampicin (HR<sub>900mg</sub>ZE HR<sub>1200mg</sub>ZE and HR<sub>1500mg</sub>ZE) and novel combinations replacing ethambutol with SQ109 or moxifloxacin (HR<sub>600mg</sub>ZQ, HR<sub>1200mg</sub>ZQ and HR<sub>1200mg</sub>ZM) were investigated. Sputum total RNA was reverse transcribed to cDNA and the 16S rRNA gene sequenced on Illumina MiSeq. Data processing and diversity comparisons between samples were analysed using Qiime 2. A total of 397 samples from 67 patients on 7 regimens were analysed.

The pre-treatment microbiome was dominated by Firmicutes (53%), Proteobacteria (13%), Bacteroidetes (13%), Actinobacteria (8%), Fusobacteria (4%) and *Streptococcus* (40%), *Neisseria* (9%), *Veillonella* (5%), *Prevotella* (4%), *Rothia* (1%) at phyla and genus level respectively. Exposure to anti-TB therapy caused a displace-replace pattern in which taxa such as Actinobacteria and *Mycobacterium tuberculosis* were consistently cleared while others recovered.

The early bactericidal activity of the moxifloxacin regimen was reflected in significant reductions of microbiome amplicon sequence variant (ASV) diversity (p=0.004) and phylogenetic diversity (p=0.007). HR<sub>1200mg</sub>ZQ only reduced ASV diversity (p=0.014) by day 14 of treatment. Among the high-dose rifampicin regimens, only HR<sub>1500mg</sub>ZE had significant reduction of ASV- and phylogenetic- diversity, p=0.027 and p=0.006 respectively.

The degree of activity against *Streptococcus* was associated with culture conversion at month-2 of treatment with 10% and 3% streptococcal reduction vis-

a-vis 27% increase for converters, non-converters and indeterminate (contaminated) culture respectively. Moxifloxacin-rifampicin<sub>1200mg</sub> combination accounted for 67% early patient culture conversion and none for rifampicin<sub>1500mg</sub>.

Our findings suggest the efficacy of anti-TB therapy is modulated by its action on the rest of the respiratory microbiome and may inform improvement of TB treatment strategies.

### TBS-OA-15 *In silico* assessment of adaptive trial design for TB regimen development

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Current tuberculosis (TB) regimen development is in dire need of innovation; the current standard of care is 50 years old while drug development strategies are slow. We identified four adaptive trial designs for late stage regimen development: phase IIC and seamless phase II/III, each with adaptive designs utilizing multi-arm multi-stage (MAMS) or Bayesian adaptive randomization (BAR).

Our objective was to evaluate the proposed trial designs using clinical trial simulations, determine optimal adaptive trial design parameters, and provide recommendations on how each design may be applied to achieve the greatest impact.

Clinical trial simulation tools were built in R using previously developed parametric survival models predicting time to culture conversion and time to relapse from patient baseline and on-treatment (biomarker) characteristics. The 9 intervention arms comprised 3 simulated regimens (Desirable, Minimal, Sub-optimal) at 3 durations (8, 12, 16 weeks), and were used to optimize trial parameters and test designs for ability to distinguish between desirable and poor regimens.

For our optimized phase IIC trial designs, sub-optimal regimens were stopped in 92% and 85% and desirable regimens stopped in 0.16% and 0.4% of simulations in the MAMS and BAR designs respectively. The optimized seamless trial designs are able to distinguish between different durations of the same regimen, where the 8 and 16-week desirable regimen was only stopped in 2.2% and 0% of MAMS simulations, and 39% and 5.6% of BAR simulations. See table for study duration and total enrollment of optimized designs.

Adaptive trial designs offer a clear advantage in simultaneously evaluating more intervention arms with similar numbers of patients in a shorter time frame.

While choice of different design approaches will depend on trial objectives, we have shown how adaptive trial designs can and will be used by international consortia for TB regimen development.

Pathway	Phase II	Phase III	Total
A: PaMZ Case Study	182 weeks 292 pts	234 weeks 1500 pts	416 weeks 1792 pts
10 Arm Simulated Trials			
A: Standard Sequential Approach*	180 weeks 1000 pts	300 weeks 1600 pts	480 weeks 2600 pts
B: Phase IIC MAMS	162 weeks 830 pts		
C: Phase IIC BAR	180 weeks 1000 pts		
D: Seamless MAMS			317 weeks 2376 pts
E: Seamless BAR			324 weeks 2440 pts

\*Pathway A was assumed to evaluate the 9 intervention arms in a non-adaptive Phase IIC design (N per arm = 100), where after a 60-week analysis and planning period three candidates were chosen to be evaluated in a separate Phase III trial (N per arm = 400).

[Table.]

### TBS-OA-16 Translational platform for predicting clinical outcomes for new combination regimens using pre-clinical and phase I data

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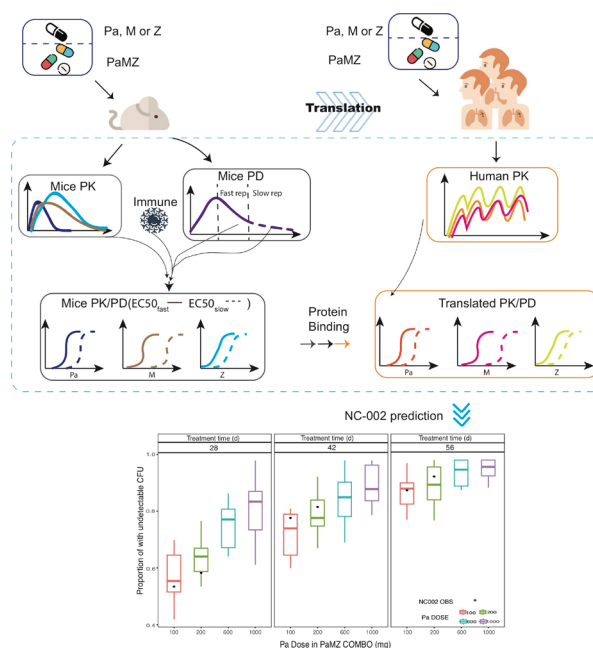
In tuberculosis (TB) drug development, the direct translation of treatment outcomes from preclinical models to human is always challenged. To enable more accurate predictions of clinical outcomes from preclinical efficacy data, a translational platform that incorporates bacterial infection, the underlying immune response, drug exposure-response in murine TB models, and clinical pharmacokinetics (PK) was developed.

Longitudinal data from 1876 infected BALB/c mice receiving no drug, dose-ranging monotherapy or combinations of Pa, M and/or Z were used for model development in NONMEM. The baseline model consisted of bacterial kinetics, and sigmoidal immune effect. PK/pharmacodynamics (PD) relationships in mice for monotherapy were explored with PD interactions added for combinations. Drug effect was explored in fast-replicating (<4 weeks since inoculation, EC50fast) and slow-replicating bacteria (>4 weeks since inoculation, EC50slow). Visual diagnostics were used for model evaluation. Translational simulations were performed using clinical PK and animal PK/PD models, with correction for protein binding.

PK/PD relationships for pretomanid (Pa), moxifloxacin (M) and pyrazinamide (Z), alone and in combination, were established in mice. EC50fast and EC50slow values

in monotherapy were estimated to be 0.32 and 3.4 for Pa, 0.0029 and 0.54 for M, 13 and 17 mg/L for Z. Less than additive effects were observed in PaMZ. EC50fast and EC50slow were re-estimated to be 1.6 and 6.5, 0.62 and 10.1, 31 and 28 mg/L for Pa, M and Z respectively, when used in PaMZ combination. The proportions of patients with negative sputum cultures while receiving 8 weeks of PaMZ with Pa at 100 or 200 mg daily were predicted using the translational platform and were consistent with the results in NC-002 trial.

Our translational platform predicted Phase IIB trial outcomes for PaMZ regimen. It represents a new tool for predicting long-term treatment outcomes for novel combinations, which could be used for drug regimen prioritization and optimization.



[Figure 1. Prediction of outcomes of PaMZ regimens (Pa=100 or 200 mg) in drug-sensitive TB patients in NC-002 trial and simulation using higher Pa doses via translational platform]

## TBSCIENCE2020 E-POSTERS:

### EP-TBS-01 Increased neutrophil count and decreased neutrophil CD15 expression correlate with TB disease severity and treatment response

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Tuberculosis remains a leading cause of death globally despite curative treatment, partly due to the difficulty of identifying patients who will not respond to therapy. Simple host biomarkers that correlate with response to drug treatment would facilitate improvement in outcomes and the evaluation of novel therapies.

In a prospective longitudinal cohort study, we evaluated neutrophil count and phenotype at baseline, as well as during TB treatment in 79 patients (50 (63%) HIV-positive) with microbiologically confirmed drug susceptible TB undergoing standard treatment. At time of diagnosis, blood neutrophils were highly expanded and surface expression of the neutrophil marker CD15 greatly reduced compared to controls. Both measures changed rapidly with the commencement of drug treatment and returned to levels seen in healthy control by treatment completion.

Additionally, at the time of diagnosis, high neutrophil count and low CD15 expression was associated with higher sputum bacterial load and more severe lung damage on chest x-ray, two clinically relevant markers of disease severity.

Furthermore, CD15 expression level at diagnosis was associated with TB culture conversion after 2 months of therapy (OR: 0.14, 95% CI: 0.02, 0.89), a standard measure of early TB treatment success. Importantly, our data was not significantly impacted by HIV co-infection.

These data suggest that blood neutrophil metrics could potentially be exploited to develop a simple and rapid test to help determine TB disease severity, monitor drug treatment response, and identify subjects at diagnosis who may respond poorly to treatment.

### EP-TBS-02 Genome-wide identification of Mycobacterium tuberculosis genetic markers associated with the history of BCG vaccination

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**Background:** Bacillus Calmette-Guérin (BCG) remains a widely used vaccine for tuberculosis (TB). Recent studies suggest that the efficacy of BCG against TB may vary with the *Mycobacterium tuberculosis* (MTB) strain. We analyzed clinical MTB isolates to identify the genetic determinants that may differentiate TB patients with and without BCG vaccination.

**Methods:** We enrolled a cohort of 4,500 adult patients with pulmonary TB in Lima, Peru between September 2009 and August 2012; participants' BCG vaccination status was assigned on the basis of the presence of a typical scar. We performed paired-end whole genome sequencing on culture-positive isolates from this group. Out of the 2010 patients with genomic sequences of MTB isolates, 1700 had BCG scars and 310 were without scar. We aligned the reads to the reference MTB H37Rv NC\_000962.3, and performed variant calling and annotation. We then conducted a genome-wide association study excluding any gene/region with a minor allele frequency of <0.01. A genetic relatedness matrix was computed to correct for population structure and a false discovery rate of <0.05 was set for the multiple comparisons adjustment.

**Results:** MTB isolates of TB patients with a BCG vaccination scar were less likely ( $p < 0.005$ ) to have variants in three genes – Rv2781c, PPE13, and hflX, but none of these genes remained significant after we adjusted for multiple comparisons.

**Discussion:** PPE13 gene is implicated in virulence and post-infection innate immune response. hflX and Rv2781c genes allow MTB to survive under hypoxic conditions, with hflX mediating transition of MTB to a dormant, drug-tolerant state. The relevance of the functions of PPE13, hflX, and Rv2781c genes to BCG-mediated protection remains unclear and may need further exploration. Validation of the notable genes in an independent dataset is warranted.

### EP-TBS-03 Characterization of regulatory B-cells for tuberculosis management

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**Background and objective:** The study of the host immune response has emerged as a potential tool for tuberculosis (TB) management. Regulatory B-cells (Bregs) are a particular subset of B-cells, able to modulate the effector immune response partly via IL-10 cytokine secretion. There is no consensus on Bregs' phenotype, as a consequence, their study supposes a major challenge. Here, we investigate and characterize different Breg phenotypes as well as their IL-10 production in TB.

**Methods:** Subjects enrolled were:

- (i) 11 patients with confirmed active TB,
- (ii) 11 individuals with LTBI, and
- (iii) 5 uninfected donors.

Peripheral Blood Mononuclear Cells (PBMCs) were isolated and stimulated with

- (i) PMA (50 ng/ml) and ionomycin (1µg/ml); and
- (ii) Mycobacterium tuberculosis lysate (5µg/ml) during 5 hours.

PBMCs were stained with the following surface anti-human antibodies: CD19-BV785, CD27-BV605, CD3-FITC, CD24-PE, and CD38-APC. PBMCs were fixed/permeabilized and then stained with IL-10-PECy7. Samples were acquired in a BD LSRFortessa cytometer. Bregs were analyzed as CD24<sup>hi</sup>CD27<sup>+</sup> and CD24<sup>hi</sup>CD38<sup>hi</sup>. Flow cytometry data were analyzed using BD FACSDiva.

**Results:** The percentage of CD24<sup>hi</sup>CD27<sup>+</sup> Breg cells in active TB patients was significantly decreased in comparison with LTBI individuals ( $p=0.0095$ ) and uninfected donors ( $p=0.007$ ). No significant differences were observed for the CD24<sup>hi</sup>CD38<sup>hi</sup> phenotype between the three different groups. IL-10 produced by CD24<sup>hi</sup>CD27<sup>+</sup> Breg cells after PMA/Ionomycin stimulation tended to be higher in LTBI individuals. Overall percentages of specific IL-10 production in Bregs were very low.

**Conclusion:** Decrease of CD24<sup>hi</sup>CD27<sup>+</sup> Bregs in active TB patients may suggest a reduction of the immune regulation, which may play a part in disease progression. Ongoing studies are focused on evaluating IL-10 production on Bregs and their progenitors; as well as assessing the regulatory capacity of each specific phenotype.

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### EP-TBS-04 Different antimycobacterial activity of alveolar macrophages in various lung legions of tuberculosis patients

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Tuberculosis (TB) is a dangerous disease caused by *Mycobacterium tuberculosis* (*Mtb*). In human lungs, *Mtb* are recognized by specific receptors on the cellular membrane, such as CD14, CD11b, and Toll-like receptor 2 (TLR-2), and engulfed by alveolar macrophages, leading to the activation of the NF-κB signaling pathway with the expression of p50 and p65 subunits and the generation of an inflammatory response with the release of many proinflammatory and antimycobacterial factors, including cyclooxygenase 2 (COX-2), reactive oxygen species (ROS), and nitric oxide produced by the enzyme inducible nitric oxide synthase (iNOS). However, *Mtb* can survive, replicate, and persist in human lungs for a long time.

In immunofluorescence assay and the Ziehl-Neelsen staining, we examined the number of *Mtb*-infected alveolar macrophages and the quantity of CD14-, CD11b-, TLR-2-, NF-κB subunits-, COX-2-, iNOS-, and ROS-positive cells in the ex vivo cell cultures (Ufimtseva et al., PLOS ONE 2018, 13:e0191918; Tuberculosis 2018, 112:1-10; Tuberculosis 2019, 114:77-90; Int J Mycobacteriol 2020, 9(2):176-84) and on the histological sections obtained from the resected lung tissues with different TB lesions: the wall of tuberculomas and the lung parts distant from tuberculomas, - for the same patients with pulmonary MDR-TB.

We found more alveolar macrophages with single *Mtb* or *Mtb* in colonies, including those with cording morphology, in the wall of tuberculomas than in the distant lung tissues of the same TB patients.

Conversely, many alveolar macrophages with the markers and antimicrobial agents examined were detected in the distant lung tissues, but not in the wall of tuberculomas. Thus, TB patients' alveolar macrophages were characterized by different microbicidal potential and contained a different number of *Mtb* in various TB legions of the same patients' lungs. Studies of the mechanisms of *Mtb* survival during TB disease are extremely important for the development of new methods for TB treatment.



### EP-TBS-05 Plasma mediators of phagocytosis in tuberculosis patients during anti-TB treatment and zinc supplementation

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Intracellular killing during phagocytosis is important in host immunity to tuberculosis. Improved treatment outcomes have been reported in TB patients receiving zinc supplement, however the underlying mechanisms are not clearly understood.

This present study assessed plasma mediators of intracellular killing in TB patients receiving zinc supplement with anti-TB regimen compared to patients receiving anti-TB regimen alone.

Sixty consenting newly diagnosed drug sensitive TB patients were recruited and randomly allocated to two groups of thirty patients. One group received zinc supplement (20mg Zinc Sulphate daily) with anti-TB drug regimen while the other group received anti-TB drug regimen alone for six months. Blood sample was collected and plasma obtained at baseline, 2, 4 and 6 months of treatment. Plasma superoxide dismutase (SOD), catalase and myeloperoxidase enzymes activities, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and nitric oxide (NO) levels were assessed by spectrophotometry. Data was analysed using Friedman and Wilcoxon signed rank tests with significance set at  $p < 0.05$ .

At 2 months, plasma SOD activity was significantly raised in patients on zinc supplement compared to baseline [0.17(0.14-0.19) vs 0.14(0.11-0.17)U/ml] whereas no significant difference in patients on treatment alone [0.15(0.11-0.23) vs 0.14(0.11-0.22)U/ml]. There were significant decreases in plasma H<sub>2</sub>O<sub>2</sub> [203.9(194.7-211.6) vs 213.3(207.0-223.0) $\mu$ mol/l], NO [18.1(14.2-29.2) vs 22.1(17.0-32.0) $\mu$ mol/l] and SOD activity [0.11(0.09-0.14) vs 0.14(0.11-0.17)U/ml] in zinc supplement group while plasma H<sub>2</sub>O<sub>2</sub>[374.8(344.7-398.9) vs 320.7(296.7-346.4) $\mu$ mol/l] and NO [12.74(8.40-19.79) vs 9.93(7.41-15.40) $\mu$ mol/l] increased with no difference in SOD activity [0.14(0.10-0.22) vs 0.14(0.11-0.22)U/ml] in patients on treatment alone at 6 months compared with baseline. Zinc supplementation during anti-TB treatment enhances mediators of phagocytosis.

### EP-TBS-06 Discerning divergent tuberculosis endotypes: a meta-analysis of individual patient data

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**Rationale:** Host response is a critical factor determining susceptibility to tuberculosis (TB). A delicate balance should be maintained between intracellular immunity against *Mycobacterium tuberculosis* (Mtb) and minimizing detrimental immunopathology. Studies have identified incongruous immune responses that can lead to a similar TB disease phenotype. Instead of envisioning that susceptibility to TB follows a singular path, we propose the hypothesis that varied host endotypes exist within the TB clinical phenotype.

**Methods and results:** Unbiased clustering analysis from 12 publicly available gene expression datasets consisting of data from 717 TB patients and 527 controls, identified 4 TB patient endotypes with distinct immune responses. The two largest endotypes exhibit divergent gene expression of metabolic, epigenetic and immune pathways.

TB patient endotype A, comprising 333 TB patients (46.4%), is characterized by increased expression of genes important for

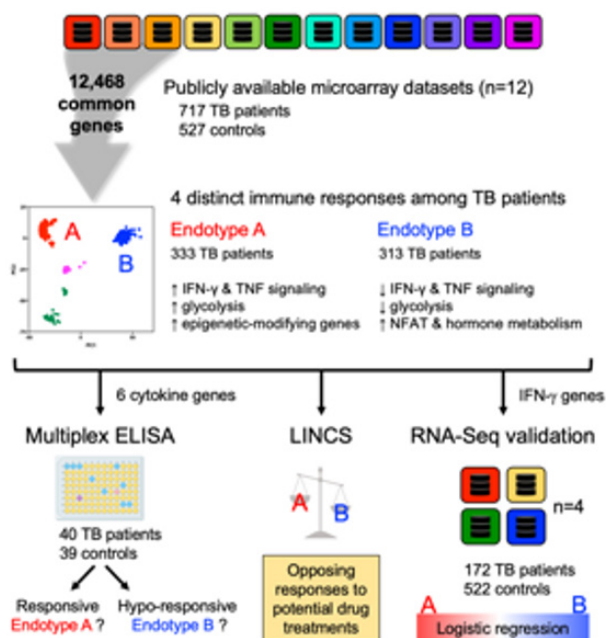
- i) glycolysis,
- ii) IL-2-STAT5, IL-6-STAT3, Type I and II Interferon IFN- $\gamma$  and TNF signaling and,
- iii) epigenetic-modifying genes.

In contrast, TB patient endotype B, comprising 313 TB patients (43.6%), is characterized by

- i) up-regulated NFAT and hormone metabolism, and
- ii) decreased glycolysis, IFN- $\gamma$  and TNF signaling.

In silico evaluation suggests therapies beneficial for endotype A could be detrimental to endotype B, and vice versa. Multiplex ELISA completed from an external validation cohort confirmed a TB patient sub-group with decreased immune up-regulation.

**Conclusions:** Host immunity to TB is not uniform, but consists of distinct and divergent metabolic, epigenetic and immune gene expression profiles that may enable stratified or personalized treatment management in the future.



[Figure 1. Experimental design. Microarray data from TB patients ( $n = 717$ ) was first normalized using RUV, then clustered using the Louvain network-based unbiased clustering algorithm as implemented in the Seurat package. The gene expression profiles of distinct TB patient endotypes were compared to healthy controls ( $n = 527$ ); pathway analysis identified divergent immune, metabolic and epigenetic pathway enrichment. Multiplex ELISA from an external validation cohort confirmed there is a sub-group of TB patients with decreased immune activation. An in silico screen of chemical compounds using the LINCS platform suggests that the two main divergent TB endotypes will respond differentially to candidate host-directed therapies. Logistic regression classification was developed for the two major endotypes and further validated on a transcriptomics (RNA-Seq) datasets of TB patients ( $n = 172$ ) and controls ( $n=522$ ).]

## EP-TBS-07 Plasma Interferon (IFN)- $\gamma$ inducible protein 10 (IP-10) levels but not the QuantiFERON Gold plus assay correlate with disease severity and paradoxical reactions in extrapulmonary tuberculosis

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**Background:** With 1,5 million deaths worldwide in 2018, tuberculosis (TB) remains a major global public health problem. While pulmonary TB (PTB) is the most common manifestation, the proportion of extrapulmonary TB (EPTB) is increasing in low-burden countries. EPTB is a heterogeneous disease entity posing diagnostic and management challenges due to the lack of reliable biomarkers. In this study we prospectively evaluated clinical data and treatment response which were correlated with different biomarkers.

**Methods:** The study was conducted at the University Hospital of Cologne. 20 patients with EPTB were enrolled. The novel QuantiFERON®-TB Gold Plus (QFT® Plus) test was performed during the course of treatment. In addition, we analyzed IP-10 levels in plasma by ELISA for up to 12 months of treatment. Clinical data was assessed prospectively and correlated to QFT® Plus and IP-10 levels.

**Results:** Plasma IP-10 levels were found to be significantly increased ( $p=0.002$ ) in patients with extensive disease compared to patients with limited disease where IP-10 levels did not differ from the healthy control. In patients with clinically confirmed paradoxical reaction (PR) a further increase of IP-10 was noted. IFN-g measured by the QFT® Plus test did not decrease significantly during the course of treatment (Antigen tube 1  $p=0.9713$  vs. Antigen tube 2  $p=0.4698$ ).

**Conclusion:** Our data demonstrate that IP-10 may be a valuable and simple biomarker for estimation of disease severity in EPTB and monitoring of the disease course in extensive forms. However, IP-10 may be less suitable for diagnostics and monitoring of EPTB patients with limited disease. The novel QFT® Plus test does not appear to be a useful marker for therapy monitoring.

### EP-TBS-08 Host immune factors related to non-multidrug resistant tuberculosis with treatment history in Vietnam

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**Background:** Recurrence of tuberculosis (TB) is one of the important issues of TB management. Although multidrug-resistant (MDR) TB is often associated with treatment history, recurrence mechanism in well-treated non-MDR TB patients remains unclear. We have investigated host immunity associated with TB recurrence.

**Methods:** Active pulmonary TB patients with previous treatment episode(s) were recruited in Hanoi, Vietnam. Before starting regimens for retreatment or MDR-TB, *Mycobacterium tuberculosis* (*Mtb*) isolates were obtained from sputum, and their peripheral blood was collected in PAXgene Blood RNA tubes (PreAnalytiX QIAGEN/BD) for total RNA extraction. The expression levels of immune-related genes were measured by the quantitative RT-PCR method using TaqMan Gene Expression Assays (ThermoFisher). We further analyzed *Mtb* by whole genome sequencing, and compared HIV-negative MDR TB patients (n=83) with non-MDR TB patients (n=125).

**Results:** Expression levels of Th1 immune genes in whole blood including *STAT1* and *IL12RB2* mRNAs, were significantly lower in non-MDR TB group than those in MDR TB group. Genetic lineages of *Mtb* strains were not associated with their mRNA expression levels.

**Conclusions:** Our results have demonstrated relatively weak host immune responses in recurrent non-MDR TB patients, although the cause-effect relationship is unknown. Thus, it is necessary to investigate their effect further after adjustment for clinico-epidemiological factors, and to identify key molecules that should be modulated as possible targets of host-directed therapies in the future.

### EP-TBS-09 Risk factors for the development of tuberculosis in children with chronic non-specific lung diseases

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Children with chronic nonspecific lung diseases are at risk of developing tuberculosis and need special attention from a phthisiatrician. Specific tuberculous inflammation joins the chronic nonspecific process and creates diagnostic difficulties.

**Objective:** To determine the risk factors for the development of tuberculosis in children with chronic nonspecific lung diseases.

Data from 100 patients with chronic nonspecific lung diseases were analyzed. The first group - children with bronchial asthma, the second - children with chronic infectious and inflammatory diseases of the respiratory tract, the third group - children with congenital malformations of the respiratory system. The results of the Mantoux test, Diaskintest, medical history were assessed. The Mantoux test was positive in the group of children with bronchial asthma in 48%, in 35.4% with infectious and inflammatory diseases, and in 29.4% with respiratory defects. Respiratory complaints were noted from an early age in 53.6% of all children with a positive Mantoux test. 63% have a history of respiratory disease. The negative result of the Mantoux test was in children with bronchial asthma in 17.1%, with infectious and inflammatory diseases in 27.0%, with respiratory defects in 35.2%. In other children, Mantoux tests were questionable.

Thus, immunodiagnostics should be a mandatory method of examining children with chronic nonspecific lung diseases, since these children often give a positive Mantoux test and are at increased risk of developing a tuberculous process. The risk of developing tuberculosis in children with chronic nonspecific lung diseases can be considered MBT infection, as well as a burdened family history. A differentiated approach to the examination of children and adolescents, taking into account the factors of the development of tuberculosis, can significantly improve the detection of patients with latent tuberculosis infection and take measures for their timely treatment and dispensary observation.

## EP-TBS-10 Polyfunctional T-cells and IL-2 production decrease during pregnancy in women with latent TB infection

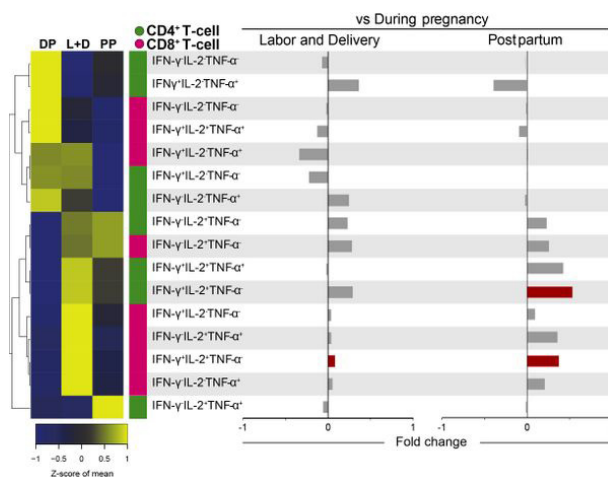
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**Background:** The highest risk time for a woman to develop active TB is immediately postpartum. Despite this well-documented epidemiology, we have a poor understanding of the relevant immune changes that occur during pregnancy to increase this risk. Our goal was to identify how cell populations change during the course of pregnancy and the postpartum period.

**Methods:** We enrolled a cohort of 20 pregnant women with latent TB infection in Pune, India. We collected PBMCs at 2nd and 3rd trimester, delivery, and 3-6 months postpartum. We performed flow cytometry on PBMCs to assess the abundance of CD4+ and CD8+ T-cells, and polyfunctionality of cell populations. The median values with interquartile ranges were used as measures of central tendency and dispersion. The Mann-Whitney U test or the Kruskal-Wallis test with the Dunn's multiple-comparison were used to compare continuous variables. The Spearman correlation rank test was used to assess correlations for each cell and each timepoint.

**Results:** Frequencies of lymphocytes expressing IFN $\gamma$ , IL2, and TNF $\alpha$  were Z-score normalized and a heatmap was designed to illustrate trends between the different study timepoints (Figure). During pregnancy, we observed increased frequency of cytokine mono-producers and double producers especially among CD4+ T-cells. At delivery, there were more polyfunctional T-cells; CD8+ T-cells were increased while CD4+ T-cells, especially those producing IL-2, were decreased compared to pregnancy. Compared to pregnancy and delivery, the highest frequency of IFN $\gamma$ -IL2+TNF $\alpha$ + CD4+ T-cells occurred postpartum. Compared to pregnancy, CD4+ IFN $\gamma$ +IL2+TNF $\alpha$ - significantly increased at delivery and postpartum; CD8+ IFN $\gamma$ +IL2+TNF $\alpha$ - also significantly increased postpartum.

**Conclusions:** IL2-producing CD4+ and CD8+ T-cells are lower during pregnancy than delivery or postpartum. Moreover, polyfunctional T-cells are also lower in pregnancy. These changes in IL-2 production and functionality of both CD4+ and CD8+ T-cells could contribute to the progression from latent TB to active TB postpartum.



[Figure. Fold-variation values were calculated during pregnancy vs. delivery and vs. postpartum timepoints. Statistically significant fold-differences ( $p \leq 0.05$ ) are highlighted in red. CD4+ and CD8+ T-cells are indicated by vertical green and red bars, respectively. DP=during pregnancy; L&D= labor and delivery; PP=postpartum.]

## EP-TBS-11 Neutrophils contribute to tuberculosis-linked inflammation and lung pathology

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TB vaccine development focuses on makers of disease prevention and neutrophil-related inflammatory mediators contribute to disease severity in active tuberculosis (ATB); making dynamics of neutrophil activity relevant to therapy and vaccine development strategies. This study aimed at characterizing neutrophil subsets in ATB patients at baseline (BL) and through standard 6-month anti-TB therapy.

Fresh whole blood from 47 patients at BL (22 followed up through therapy) were stimulated for 2 hours with PMA, ESAT6/CFP10 fusion protein (EC) or H37Rv whole cell lysate (LYS). An unstimulated control was used to account for basal activation levels. Cells stained with surface markers, lysed/fixed and permeabilized were stained intracellularly prior to flow cytometry. Neutrophil were classified by Side Scatter, CD14, CD16 and CD62L expression. Neutrophil oxidative index (NOI); CD11b, IL10 & TNF- $\alpha$  expression levels were quantified. The Ralph Score allowed assessment of lung disease severity. CD14- neutrophils were either immunosuppressive: ISH (CD16+CD62L-) and ISD (CD16dimCD62L-); or pro-inflammatory: PIH (CD16+CD62L+) and PID (CD16dimCD62L+).

There were significantly fewer circulating granulocytes at 6M vs. BL ( $<0.0001$ ) with their NOI following PMA stimulation showing significant reduction ( $p=0.0083$ ) after therapy. Besides, NOI after PMA stimulation distinguished between patients with mild vs. severe lung damage at BL for granulocytes and ISD ( $p=0.0186$  and  $p=0.0301$ , respectively). Furthermore, EC-stimulated ISD expressed significantly more CD11b and TNF- $\alpha$  ( $p=0.0006$  and  $p=0.0005$ ) at BL vs. 6M. In contrast, LYS-stimulated PID expressed significantly less CD11b ( $p=0.0016$ ) at BL vs. 6M.

In conclusion, we observed that neutrophil inflammatory mediators influence treatment response and disease severity in ATB.

### EP-TBS-12 Association of neutrophil-derived inflammatory mediator levels with lung pathology in active tuberculosis at diagnosis

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**Background:** Neutrophils are the first cells recruited to the lung during active TB disease and are likely to contribute to TB-induced lung damage considering their extensive inflammatory potential.

The aim of this study was to assess the variation of neutrophil-related soluble inflammatory mediators in relation to the degree of lung pathology in patients with active pulmonary TB (ATB).

**Methods:** Sputum and plasma samples were obtained from 138 ATB patients. These were classified into mild ( $n=57$ ) or severe ( $n=61$ ) lung pathology based on chest x-ray Ralph scores. Samples were analysed for GM-CSF, IFN $\gamma$ , TNF, IL8, IL10, IL12, MMP1, MMP3, MMP8, MMP9, MPO, S100A8 and S100A9 using Bio-Plex 200 system (Bio-Rad, Belgium). The Wilcoxon rank sum test was used to compare medians between severity groups.

**Results:** Plasma levels of MMP1 ( $p=0.017$ ), MMP8 ( $p=0.0018$ ), IL8 ( $p=0.0071$ ), IL12/23(p40) ( $p=0.0065$ ) and IFN $\gamma$  ( $p=0.038$ ) were significantly higher in severe than in mild groups at presentation. Sputum MMP8 ( $p=0.021$ ) was significantly higher in severe than in mild groups at BL. In contrast, sputum MPO ( $p=0.00015$ ) and IL10 ( $p=0.011$ ) were lower in the severe group.

**Discussion and conclusions:** Neutrophils are the major MPO-producers hence, patients with lower MPO in sputum (severe group) at presentation suggest lower neutrophil densities and/or reduced activity of recruited neutrophils into the lungs. The lower IL10 levels in this group also suggest decreased anti-inflammatory activity. Moreover, enhanced systemic levels of MMP8 (neutrophil collagenase) in sputum and plasma as well as MMP-1 (in

sputum) in the severe group suggests that these MMPs are indicators of increased lung pathology. For the former, this also suggests enhanced activation and degranulation of circulating and infiltrating neutrophils.

In conclusion, levels of (neutrophil) mediators are associated to the severity of lung damage in ATB.

### EP-TBS-13 Characterising the BCG-induced antibody response for antigen discovery

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Immunological assessment of BCG vaccination has focussed on induction of cell-mediated immunity. While a growing body of evidence indicates a role for antibodies in immunity from TB, there is a paucity of literature on the humoral response to BCG vaccination. Studying the BCG response in relation to outcomes of mycobacterial challenge may be particularly valuable in determining factors contributing to protection.

We take an unbiased approach, using whole-protein microarrays spanning the entire proteome of *M.tb* to identify targets recognised by BCG-induced antibodies in serum samples from humans, non-human primates (NHP) and cattle. Responses are related to protection from *M.tb* or BCG challenge in matched NHP and cattle respectively.

We report preliminary findings regarding the top protein targets of BCG-induced IgG across species ranked by absolute reactivity and fold change in reactivity following vaccination. We find that top-ranked proteins differ by species and by route of BCG administration in NHP, with higher reactivity in the intravenous (IV) vaccinated group and in particular the two most protected animals. Our data indicates that route of vaccination alters target antigen repertoire and suggests potential associations between IgG antigen specificity and improved protection from challenge.

Following validation studies, new vaccine constructs using proteins of interest will be tested in mouse challenge experiments. Insights into the BCG-induced immune response could be key to informing the design of an efficacious new TB vaccine which may benefit from targeting humoral as well as cell-mediated immunity.

This work was funded by a VALIDATE Fellowship to RT.

### EP-TBS-14 ESAT-6 / CFP-10-stimulated metabolic activity of pleural fluid cells if cured tuberculosis or TB / HIV

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We show (E.R.J. 2019; 54: Suppl. 63, PA3013) that the metabolic response of pleural fluid cells (PF) to stimulation with MBT antigens depends on the activity of tuberculosis.

To assess the effect of specific stimulation in other clinical cases of tuberculosis, we studied phagocytosis of neutrophils and IFN-gamma in PF in 20 patients with tuberculosis: patients operated on for lung caseoma (LC, n = 6) and patients with active pulmonary tuberculosis and HIV (TB-HIV, n = 14).

The phagocytosis was determined in a native sample (NS) of PF, a native sample after incubation at t0 37.0 C0 (NSI), and after incubation at t0 37.0 C0 with – ESAT-6/CFP-10 (AgS). IFN-gamma was measured at baseline and after specific stimulation in vitro.

Data are presented as median and 25%-75% range. Mann-Whitney and Kruskal-Wallis test were used to compare of variables.

Phagocytosis was significantly enhanced in granulocytes in NS in LC group compared to the TB-HIV group: 1208.1 in  $\mu$ l and 37.6 in  $\mu$ l, respectively ( $p = 0.016$ ).

Phagocytosis in granulocytes in the NSI and AgS in LC group was significant decrease to compare NS: 249.2 and 281.8 in  $\mu$ l ( $p = 0.049$ ).

Incubation of the native PF of TB-HIV group led to a 2-fold decrease of capacity to phagocytose in the TB-HIV group to 17.3 in  $\mu$ l to compare NS, phagocytosis in the AgO was significantly higher - 33.4 in  $\mu$ l ( $p = 0.046$ ). The level of IFN- $\gamma$  at baseline in LC and TB-HIV groups were: 7.1 pg/ml (5.9 – 14.4) and 375.6 pg/ml (22.64 – 846.9) ( $p > 0.05$ ). IFN- $\gamma$  levels did not change significantly after specific stimulation.

The metabolic response of pleural neutrophils to ESAT-6/CFP-10 stimulation decreases when the main focus of tuberculosis is removed.

Pleural granulocytes from HIV-TB patients initially have a decreased ability to phagocytosis, but retain it when stimulated with ESAT-6/CFP-10.

### EP-TBS-15 Blood-based biomarkers of tuberculosis in children integrating metabolomic and transcriptomic data

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**Background:** Pediatric tuberculosis (TB) remains a major global health problem. Improved pediatric diagnostics using readily available biosources are urgently needed.

**Methods:** We used liquid chromatography-mass spectrometry to analyze plasma metabolite profiles of Indian children with active TB (n=16) and age- and sex-matched, Mycobacterium tuberculosis-exposed but uninfected household contacts (n=32). Metabolomic data were integrated with whole blood transcriptomic data for each participant at diagnosis and throughout treatment for drug-susceptible TB.

**Results:** A decision tree algorithm identified 3 metabolites that correctly identified TB status at distinct times during treatment. N-acetylneuraminate achieved an area under the receiver operating characteristic curve (AUC) of 0.66 at diagnosis. Quinolinate achieved an AUC of 0.77 after 1 month of treatment, and pyridoxate achieved an AUC of 0.87 after successful treatment completion. A set of 4 metabolites (gamma-glutamylalanine, gamma-glutamylglycine, glutamine, and pyridoxate) identified treatment response with an AUC of 0.86. Pathway enrichment analyses of these metabolites and corresponding transcriptional data correlated N-acetylneuraminate with immunoregulatory interactions between lymphoid and non-lymphoid cells, and correlated pyridoxate with p53-regulated metabolic genes and mitochondrial translation.

**Conclusions:** Our findings shed new light on metabolic dysregulation in children with TB and pave the way for new diagnostic and treatment response markers in pediatric TB.



### EP-TBS-16 Identification of TGF- $\beta$ 1 in pleural tuberculosis: the possible role in fibrosis

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The inflammatory reaction in pleural cavity in response to Mycobacterium tuberculosis infection has an action on several cell types such as the mesothelial cell whose respond to injury and its ability to maintain tissue integrity is crucial for normal tissue repair or for the formation of fibrosis. It is known that in fibrotic diseases, the main characteristic is the increase in the production of transforming growth factor beta 1 (TGF- $\beta$ 1).

Thus, the aim of this study was to evaluate the levels of TGF- $\beta$ 1 in the pleural fluid (PF) and peripheral blood (PB) of patients with exudative pleural effusion due to pleural tuberculosis (PITB) and other non-TB diagnoses (NTB).

Seventy four patients (mean age 51 years) were recruited at the Pulmonology and Tisiology Service from Pedro Ernesto University Hospital/UERJ, Rio de Janeiro, RJ, Brazil. Of these, 44 (59.45%) male and 30 (40.5%) female; 41 (55.4%) were diagnosed as PITB and 33 (44.6%) were classified as NTB (24 malignancies, 02 lupus, 02 lymphomas, 01 chylothorax, 02 empyema, 02 undefined DPE). TGF- $\beta$ 1 levels were measured by enzyme-linked immunosorbent assay (ELISA).

We did not observe a significant difference in the levels of TGF- $\beta$ 1 in the serum of PITB patients compared to the NTB group ( $p > 0.05$ ). In contrast, we found high levels of TGF- $\beta$ 1 in the PF of PITB patients (112.5pg / mL  $\pm$  10.6) compared to NTB (67.09 pg / mL  $\pm$  11.05) ( $p = < 0.005$ ). When we compare the levels of TGF- $\beta$ 1 between serum and PF, we found higher levels in serum ( $p < 0.0001$ ) in both groups.

Our data suggest a possible contribution of this molecule to the pathogenesis of the disease and/or fibrosis in patients with PITB. The association with other profibrotic factors may be a possible tool to aid in the identification and progression of fibrosis in this pathological situation.

### EP-TBS-17 Analysis of serum microRNAs as pulmonary tuberculosis biomarkers

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Pathogenesis of tuberculosis (TB) is highly complicated and a sputum-based measurement for tuberculosis are insufficient to discriminate disease stage (active or latent TB) and to support optimal detection of treatment outcome (cure, failure or relapse). Recently, microRNAs (miRNAs) have been considered as diagnostic biomarkers related to intracellular pathogens. Previously, we determined more than 2-fold up-regulation of miR-4449, miR-548a-3p, miR-4284, miR-146a-5p, miR-378, and miR-9-3p in THP-1 infected with Mycobacterium tuberculosis H37Rv and K (Korean strain, Beijing type).

In this study, we aimed to determine circled microRNAs (c-miRNAs) could use as blood biomarkers for detection of TB and differentiate TB stage.

A total 36 individuals were enrolled, 11 healthy individuals (TST(-) and IGRA(-)), 13 LTIB individuals (TST(+) or IGRA(+)) and 12 active pulmonary TB patients with no more than 2 weeks of anti-TB treatment. Total RNAs were extracted from all participants with Advanced miRNA mini kit (QIAGEN). C-miRNAs were screened and analyzed using small RNA sequencing. The 14 and 46 c-miRNA were more than 2-fold up- and down-expressed in the active TB and LTBI group compared to healthy controls, respectively. The 71 c-miRNA were differentially expressed in active TB group compared with LTBI group.

It was observed that the expression miR-4284, miR-548a-3p and miR-4301 specifically increased in active TB group. The has-miR-549a-3p (up), hsa-miR-143-3p (up) and has-miR-4301 (down) were significantly regulated in active TB group compared to LTBI group.

Our results suggest that first, c-miRNAs are highly stable in blood serum. Second, c-miRNAs express differently in TB stage and are expected as new diagnostic biomarkers for discrimination of active TB and LTBI.

## EP-TBS-18 Up-regulated programmed death protein 1 expression on CD4 T cells in patients with MDR-TB associated with lung lesion and mycobacterial load

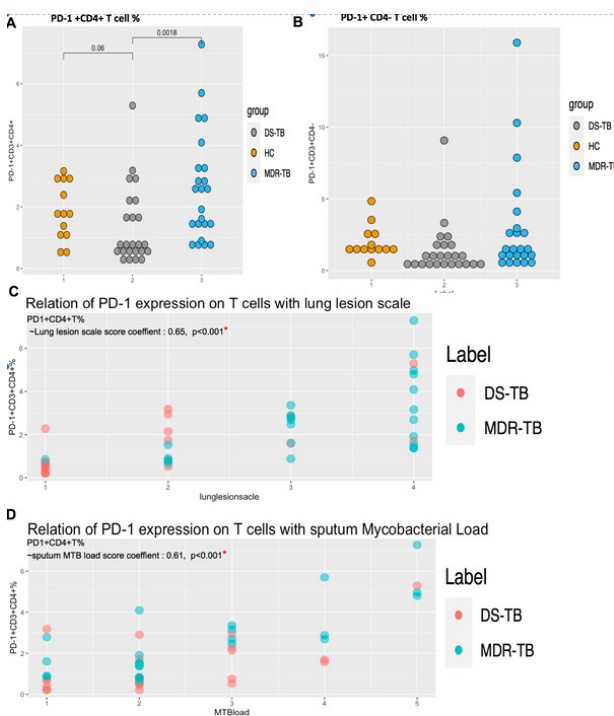
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**Background:** Multidrug-resistant TB (MDR-TB) is challenging the end-TB goal worldwide for the poor treatment outcomes. Our previous study has suggested that CD4+T cell subsets were remarkably unregulated in MDR-TB patients. However little is known about the irregular adaptive immunity mechanism in MDR-TB. The inhibitory coreceptor programmed cell death 1 (PD-1), is transiently induced upon T cell receptor (TCR) engagement and T cell activation.

Our pilot study focused on PD-1 expression on periphery T cells and their relation with clinical severity in patients with MDR-TB.

**Methods:** We measured PD-1 expression on CD4+ and CD4- T cell subsets in periphery blood mononuclear cell (PBMC) from blood samples of healthy donors (N=13), DS-TB patients (N=24), MDR-TB patients (N=23) by flow cytometry and surface antibody staining. Multiple Linear Regression was used to identify the coefficient of possible clinical parameters (including chest imaging, sputum smear, and clinical symptom) with PD-1 expressed T cells frequencies in PBMC of TB patients.



[Figure 1.]

**Results:** PD-1+CD4+T cells percentage in PBMC of MDR-TB group were statistically higher than DS-TB group (Figure 1 A,B). Among all the clinical parameters,

the number of lung lesions was identified related to PD-1+CD4+T cell frequency with coefficient 0.65 (Figure 1 C) and the sputum mycobacterial load were significantly related to PD-1+CD4+T cell frequency with coefficient 0.61 in TB patients (Figure 1 D). The lung lesion number but not mycobacterial load was identified related to PD-1+CD4-T cell frequency with coefficient 1.09 in TB patients.

**Conclusion:** Our findings suggested PD-1 expression on CD4+T cells could play a role in T cell response disorder in MDR-TB patients. Higher PD-1 expression on CD4+ T cells were associated with exacerbated Mycobacteria replication in lung foci and lung tissue damaging, which still need further study for validation and might provide a potential treatment target for MDR-TB patients.

## EP-TBS-19 Malnutrition affects levels of vascular endothelial growth factor levels among children and adolescents with pulmonary tuberculosis?

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**Background:** Pulmonary tuberculosis (PTB) in young children is paucibacillary, indicating a diagnostic challenge. The vascular endothelial growth factor (VEGF) is a biomarker used as a diagnostic tool. Malnutrition, in turn, consists of a common co-affection in these cases, which influences the immunological response. Our aim is to analyze if malnutrition affects VEGF levels among patients with PTB and without PTB (NPTB).

**Methods:** A cross-sectional study was carried out with patients from 0 to 19 years old diagnosed with PTB and NPTB (asymptomatic individuals or with pneumonia) from September/2014 to February/2018. The diagnosis of PTB was confirmed if the patient had an Xpert molecular test and/or a positive culture for *M. tuberculosis*. Malnutrition was determined by the variable height x age, with a z score <-1, using the WHOAnthroPlus®. Serum VEGF levels were measured by tests of multiplex microspheres. The data were analyzed using the GraphPad Prism v.8.0 program (GraphPad Inc., San Diego, CA). Statistical significance was p<0.05.

**Results:** Fifty-five patients were included in the study, 11 malnourished (5 PTB and 6 NPTB) and 44 not malnourished (13 PTB and 31 NPTB). VEGF levels in not malnourished were higher in the TB group compared to the NPTB group (p<0.0001). Curves ROC analysis dem-

onstrated high diagnostic power to differentiate PTB and NPTB, with an AUC of 0.84 (0.71 - 0.94;  $p < 0.0001$ ) for not malnourished, and AUC of 0.53 (0.20 - 0.87;  $p < 0.0001$ ) for malnourished. The cutoff value of VEGF for not malnourished was  $>1,132$  pg/mL, with sensitivity of 84% and specificity of 77%, and for malnourished patients was  $>1,259$  pg/mL, with sensitivity of 80% and specificity of 50%.

**Conclusion:** VEGF is a promising biomarker to differentiate PTB from NPTB in children and adolescents, but it should be used with caution among malnourished patients, needing more studies in the area, mainly prospective studies.

### EP-TBS-20 Towards identification of protein markers of *Mycobacterium tuberculosis* H37Rv extracellular vesicles (EV)

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*Mycobacterium tuberculosis* (MTB) release extracellular vesicles (EV) which contain various molecules to impair functions of infected macrophage and circulate bacterial components to modulate the host immune response. EVs are being investigated as new vaccines and biomarkers but currently they require confirmation by electron microscopy.

This study aimed to identify candidate protein markers of EVs by 1) systemic literature review on PubMed and 2) proteomic bioinformatics analysis of published complex antigenic preparations of MTB EVs, compared with classic complex antigens, protein purified derivative (PPD) and antigen 60 (A60).

Of the 127 articles on bacterial vesicles retrieved and reviewed, 6 articles focused solely on mycobacteria, with HSP90, and LpqH proteins found to be prominent across the literature on MTB EVs. On bioinformatics analysis, 142 (49.5%) proteins were unique to EVs, with most proteins enriched for ribosomes and translation processes.

However, 68 (9.67%) proteins were commonly found in EV, A60 and PPD, which were enriched for binding and catalytic activity, with significant predicted protein-protein interaction among heat-shock proteins and ribosomal proteins, including key proteins associated with EVs such as LpqH, LprG and LprA.

Additionally, 38 (8.53%) proteins were found only in EV and PPD, and 39 (6.44%) proteins found only in EV and A60, the former associated with the extracellular region such as ESAT-6 (EsxA/B) and the latter associated with cell wall and ribosome, such as 30S and 50S proteins.

This analysis suggests that common EV proteins such as heat-shock proteins and LpqH are also present in A60 and PPD, and ribosomal protein unique to EVs may be further explored to identify more definitive markers of EVs and facilitate further research in this area.

### EP-TBS-21 Increased frequency of CD39+ regulatory T cells in the pleural fluid of patients with Tuberculosis in comparison to other exudative causes

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**Introduction:** Regulatory T cells (Treg) play an important role in the tolerance and immune homeostasis preventing tissue damage and functional loss. A scarce literature is found regarding the heterogeneity of Treg markers in Pleural Tuberculosis (PTB), the most common extrapulmonary manifestation of TB.

**Objectives:** The aim of the present study was to phenotypically characterize Tregs in the pleural fluid and peripheral blood from PTB patients and their association to clinical findings in comparison to other causes of exudative pleural effusions.

**Methods:** Mononuclear cells of peripheral blood and pleural fluid from PTB patients ( $n = 11$ ) and NTB ( $n = 11$ ) were cultured with or without anti-CD3 stimulus. Total Tregs (Treg CD25<sup>high</sup>): CD4<sup>+</sup> CD25<sup>high</sup> FOXP3<sup>+</sup> and memory Tregs (Tregmem): CD4<sup>+</sup> CD25<sup>high</sup> CD127<sup>low</sup> CD45RO<sup>+</sup> FOXP3<sup>+</sup> and conventional T CD4<sup>+</sup> cells (Tconv): CD4<sup>+</sup> CD25<sup>+</sup> CD45RO<sup>+</sup> FOXP3<sup>-</sup> were analyzed by Flow Cytometry. Additionally, Treg CD39<sup>+</sup> was also evaluated.

**Results:** We observed high frequencies of both Treg CD25<sup>high</sup> and Tregmem in the pleural fluid when compared to blood in PTB patients. Treg CD25<sup>high</sup> CD39<sup>+</sup> and Tregmem CD39<sup>+</sup> also exhibited high frequencies in pleural fluid compared to the blood of PTB patients. Moreover, a greater proportion of Treg CD25<sup>high</sup> CD39<sup>+</sup> by conventional T cells was found in the pleural fluid from PTB group in comparison to blood or NTB pleural fluid. Interestingly, ultrasound data from pleural cavity has revealed that pleural effusions showing less complexity were associated with higher frequencies of Treg CD25<sup>high</sup>, Tregmem and Tregmem CD39<sup>+</sup>.

**Conclusions:** Although preliminary, our data provide new insights on the participation of Tregs in the immunopathology of PTB, suggesting that increased frequencies of Treg expressing immunosuppressive markers over conventional T cells may favor a less complexity of pleural effusions.

## EP-TBS-22 Longitudinal analysis of M. tuberculosis-specific T cell responses demonstrates dynamic T cell responses to ESAT-6 and CFP-10 during pregnancy independently of mitogen responses

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**Background:** Tuberculosis (TB) is a leading infectious cause of death among women aged 15-45 years. Susceptibility to *Mycobacterium tuberculosis* (Mtb) may increase during the peripartum period, but the impact of pregnancy on Mtb-specific T cell responses is poorly understood.

**Methods:** The Partners PrEP and Partners in Prevention trials enrolled >8100 couples in Sub-Saharan Africa with serodiscordant HIV status and collected clinical data and peripheral blood longitudinally over 24-36 months. To evaluate the impact of pregnancy on Mtb-specific T cell responses, we identified individuals who became pregnant during the study period with samples available pre-, post-, and during pregnancy and measured frequency of ESAT-6/CFP-10-specific (indicating Mtb infection) and mitogen-induced IL-2, IFN $\gamma$ , and TNF from CD4+ and CD8+ T cells by intracellular cytokine staining and stratified them by pregnancy stage.

**Results:** We included 118 samples from 48 women (median age 27.3 years, n = 18 with HIV) at 71 visits before or after pregnancy and 47 during pregnancy (median gestational age 26.9 weeks [IQR 12.7-30.9]). Among 22 individuals with detectable ESAT6/CFP10-specific CD4+IFN $\gamma$ + responses, we found significantly fewer ESAT6/CFP10-specific IL-2+CD4+ cells and a trend toward fewer TNF+CD4+ cells during the third trimester when compared with pre- and post-pregnancy (mean %IL-2+CD4+: 0.16 pre- or post-pregnancy, 0.07 third trimester; p=0.04, GEE with Gaussian link).

We observed significantly diminished IFN $\gamma$ +CD4+ responses to mitogen (p=0.02) but increased IL-2+CD4+ responses (p=0.008) and IL-2+CD8+ T cells (p=0.004) during pregnancy.

**Discussion:** Our preliminary analysis shows dynamic T cell responses during pregnancy, and selectively altered Mtb-specific responses during the third trimester. To our knowledge, this is the first longitudinal analysis of TB-specific T cell responses that includes pre-pregnancy samples and samples from each trimester of pregnancy.

## EP-TBS-23 Serum cytokine profile as biomarker for multi-drug resistant tuberculosis

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The rising prevalence of multidrug resistance tuberculosis (MDR-TB) associated with longer treatment duration and reduced treatment success compared to drug susceptible TB (DS-TB) is a major setback to TB control. In addition to early diagnosis, biomarkers to monitor response to treatment of patients with MDR TB are urgently needed. Serum cytokine levels are helpful in detecting *M. tuberculosis* infection.

We therefore hypothesized that MDR-TB could be characterized by unique serum cytokine signature that could be useful as immunological biomarkers for development of MDR-TB and monitoring of early treatment effect.

In this study, we compare the serum cytokine levels of the inflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-12p70, IL-17A and granzyme B) and the anti-inflammatory cytokines (IL-10, IL-6, and IL-4) among 25 MDR-TB, 21 DS-TB patients and 21 healthy controls (no TB) using the Human Magnetic Luminex Multiplex Immunoassay (Luminex, Austin, TX, USA). The sensitivity and specificity of these markers were evaluated by receiver operating characteristic (ROC) curve analysis. Serum concentrations of IFN- $\gamma$ , IL-4 and TNF- $\alpha$  were significantly elevated in DS-TB and MDR-TB compared to healthy controls (P=0.01, P=0.0001, P=0.0001 respectively).

Serum IL-10, IL-6 and IFN- $\gamma$  levels were higher in DS-TB compared to MDR-TB while levels of TNF- $\alpha$  and IL-4 were higher in MDR-TB compared to DS-TB. The ROC curve analysis indicated IL-4, TNF- $\alpha$ , Granz B had significant sensitivity in differentiating among MDR-TB, DS-TB and Healthy controls AUC: 0.827 (P= 0.009), 0.759 (P= 0.003), 0.728 (P=0.009) respectively.

Multiple serum cytokines have the potential to be exploited as TB biomarkers and may provide a formidable tool to distinguish MDR-TB or DS-TB from healthy controls with no-TB. However, in this study only high levels of the pair of cytokines, IFN- $\gamma$  and IL-4 appear to be an indicator of MDR-TB compared to DS-TB.

## EP-TBS-24 Reanalysis and validation of tuberculosis genes signature in blood and pleural fluid from patients with exudative pleural effusion

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**Introduction:** Pleural Tuberculosis (PITB) is the most common presentation of extrapulmonary TB. Recently, we have shown a predominance of Th1 cytokine profile in pleural fluid (PF) of PITB patients which could distinguish from other non-TB exudative causes. These data suggest an active immune response related to host defense in pleural cavity and open views for new biomarkers identification.

**Objectives:** Herein, we decided to identify a set of genes previously described in Pulmonary TB in order to validate a transcriptional signature in PITB clinical specimens.

**Methodology:** First, target genes were selected using recursive feature elimination by bioinformatics reanalysis of the public database from Bloom et al., PLOS ONE 8(8), 2013. In a second step, patients with exudative pleural effusion were prospectively recruited from Pedro Ernesto University Hospital, Rio de Janeiro State University, Rio de Janeiro, Brazil. Whole blood and PF were collected in PAXgene tubes after thoracentesis procedures. Transcriptional analysis was performed by Real Time RT-PCR (qRT-PCR).

**Results:** A top-ten candidate genes was identified which showed an accuracy of 89.5% to distinguish TB versus non-TB cases: CARD17, BHLHE40, FCGR1A, BATF2, STAT1, BTN3A1, ANKRD22, C1QB, GBP2 and SEPTIN4. Cohort of patients consisted of 28 male and 20 females, grouped as PITB (n = 24) and non-TB (n = 24). After the qPCR-RT analysis, CARD17, BTN3A1 and C1QB genes have shown significant differential expression between PITB and non-TB groups, in both PF (p<0.0001; 0.0001; 0.001) and blood (p=0.114; 0.175; 0.001) samples. Moreover, we observed that CARD17 and BTN3A1 gene expression were higher in PF of PITB than non-TB patients. C1QB expression showed an inverse behavior, being higher in PF from non-TB.

**Conclusion:** Our findings showed that the identification of biomarkers at the Mtb infection site may contribute to differential diagnosis among exudative pleural effusion, allowing to accelerate the beginning of anti-TB therapy.

## EP-TBS-25 TimBre, cough based screening of pulmonary tuberculosis using machine learning that is explainable and interpretable

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Shortness of breath & cough are the main reasons to visit a clinic world over. While Acute & Chronic cough are not mutually exclusive, Chronic cough is a manifestation of many diseases & its “timbre” changes even with voluntarily elicited cough & is different for each pathological condition and also varies between the same subject. 95% of chronic cough entails Post Nasal Drip Syndrome (PNDS), Bronchial Asthma, Gastroesophageal Reflux Disorder (GERD), Chronic Bronchitis, Bronchiectasis & Angiotensin Converting Enzyme Inhibitor users (ACE) & Pulmonary Tuberculosis (TB) falls under the remaining 5% along with a few others.

The cough pattern is very distinctive in that it is Bitonal which may also mimic the cough sounds of a Bronchial compression. Cough based analysis has been done in the past for TB which was confined to spectral analysis while clinical & demographics were not considered in the analysis which is extremely important in the post COVID-19 world.

The global numbers of 10 Million TB cases is most likely to double if the necessary interventions are not made. The current solution is complimentary in nature in that, cases can be screened within minutes & channeled for a confirmatory diagnostic test in a developing high burden country (HBC) that has a need to accomplish SDG goals. Most importantly, avoid the infection of their kith & kin which exposes a vulnerable situation during a pandemic.

Results of a multi-site double blinded clinical study at NH, Bangalore for cohort2 are represented in the table image for 500 subjects that achieved a sensitivity of 80% & a specificity of 92% paving way for it to be a screening solution that can be implemented at the last mile by a healthcare worker.

Statistic	Value	95% CI
Sensitivity	80.00%	28.36% to 99.49%
Specificity	92.54%	89.77% to 94.75%
Positive Likelihood Ratio	10.72	6.24 to 18.43
Negative Likelihood Ratio	0.22	0.04 to 1.25
Disease prevalence (*)	1.05%	0.34% to 2.44%
Positive Predictive Value (*)	10.26%	6.23% to 16.42%
Negative Predictive Value (*)	99.77%	98.69% to 99.96%

[Table.]

**EP-TBS-26 HbA1C as prognostic factor in PTB**

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**Aim:** To study the effect of HbA1C levels on sputum conversion in sputum positive AFB patients with BMI >25 kg/m<sup>2</sup>

**Methodology:** Patients were divided into two groups:

- Group A with HbA1C between 4.5-6.5%
- Group B with HbA1C more than 6.5%

Patients were started on category 1 ATT and weekly sputum AFB staining was done till sputum AFB became negative.

**Sample size:** 50 patients

**Inclusion criteria:**

- Patients consenting for study
- Patients with newly diagnosed PTB
- Patients with BMI>25 kg/m<sup>2</sup>
- Patients on category 1 ATT
- Patients more than 30 years of age
- Patients with type 2 diabetes

**Exclusion criteria:**

1. Patients not consenting for the study
2. Patients diagnosed with MDR/XDR TB
3. Patients with type 2 diabetes on insulin

**Results:**

1. Study had male predominance with 35 males and 15 females
2. Mean (SD) age was 38.4
3. Patients included in Group A were 28/50
4. Patients included in group B were 22/50
5. Sputum conversion time was shorter in Group A patients:
  - a. 18 patients came sputum negative in 3 weeks of starting ATT
  - b. 10 patients became sputum negative in 4 weeks of starting ATT
6. Sputum conversion time in Group B patients:
  - a. 14 patients became sputum negative in 6 weeks
  - b. 6 patients became sputum negative in 8 weeks
  - c. 2 patients developed MDR-TB

**Conclusion:** It can thus be said that HbA1C plays a significant role in prognosis and predicting the overall recovery in sputum positive PTB patients with BMI >24kg/m<sup>2</sup>.

**EP-TBS-27 Better intradermal delivery for bacille Calmette-Guérin (BCG) vaccine by microneedles in healthy adults of S. Korea**

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The conventional route of BCG vaccination is an intradermal delivery by needle and syringe, which demands a skilled medical staff with experience. To reduce any complexity of intradermal injection, the Micron-Jet600™ device, enabling controlled delivery depths with minimal pain and lowered risk associated with handling needles during injection, was lately introduced to use for Mantoux Tuberculin Skin Test (TST) or BCG vaccination. In this study we aimed to evaluate safety and immunogenicity of BCG vaccine delivery using novel microneedle compared to those using conventional needle in healthy adults of S. Korea.

A prospective, randomized, open-label, and single-centered clinical study was conducted from April through September 2019, enrolling healthy adults of S. Korea, aged between 19 to 35 years without any evidence of tuberculosis infection and disease. All eligible study participants were randomly assigned to receive one dose (0.1mL) of BCG vaccine either by the microneedle or by the conventional needle. We assessed adverse events associated with microneedle injections. Also, in terms of immunogenicity, TST was measured before and after BCG vaccination, along with observation of BCG scar formation in two groups.

A total of fifteen healthy adults were enrolled and randomly received BCG vaccination either with the microneedle (n=7) or with the conventional needle (n=8). The study showed there was no adverse events or no serious adverse events (SAEs) associated with microneedles for 12±1 weeks. In terms of immunogenicity induced by BCG vaccination, 80% of all vaccines were converted to TST positive, and all of them had BCG scar formation, regardless of the type of delivery devices.

We expect the novel microneedle device may contribute to reduce adverse events resulting from the technical difficulties of intradermal vaccination in infants subjected to BCG vaccination. Further clinical evaluation for infant BCG immunization might be necessary, carefully observing their effectiveness in practice.



### EP-TBS-28 Multiplex biomarker assay for detection of mycobacterium tuberculosis

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Over a third of the world's population is infected with *M. tuberculosis*. Annually, more than 10 million of these individuals develop clinical symptoms and about 2 million dies of tuberculosis. India is ranked at the top of tuberculosis (TB) burdened countries with 24% of TB patients in the world, and there are 2.2 million new cases per year. The infected host typically mounts a vigorous immune response. Nevertheless, 10% of all infections result in active disease within two years. Another 10% of cases may experience disease after a latent phase spanning many years.

IGRAs and TSTs have been used worldwide as an aid in diagnosing LTBI. Limitations for use of TSTs are the proper administration of tuberculin-purified protein derivative (PPD), false-positive due to non-tuberculosis mycobacteria or BCG vaccination. Serology tests were attempted to fill the gap in active tuberculosis (TB) diagnosis. Using the bead-based multiplex immunoassay approach, the present test showed antibody profiles to several *M. tuberculosis* antigens resulting in a multiplex TB serodiagnostic test that has demonstrated the ability to perform at the consistently high sensitivity and specificity.

The field validation studies in clinical settings show this multiplex TB serodiagnostic test to be robust and accurate. A multiplex microbeads immunoassay based platform Becton-Dickinson (BD) satisfies all the above requirements useful for infectious disease diagnostic. RU-1 minimally invasive, rapid and cost-effective, can be performed on plasma or serum.

The sensitivity of the assay (96% for sputum smear-positive, 88% for sputum smear-negative, culture positive, 91% overall) and specificity (96%) compared quite favourably to the numbers from the Cepheid Xpert MTB/RIF trials. The specificity of 96% was based on testing COPD patients. COPD symptoms can look much like TB, so this population represents a control group that would be encountered during clinical deployment of this panel.

### EP-TBS-29 Role of the chemokine receptor CXCR3 in the recruitment and retention of lung resident memory T cells following a pulmonary TB vaccine

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*Mycobacterium tuberculosis* (*Mtb*) is a major human pathogen, and current vaccination strategies are ineffective at preventing transmission. Recent evidence indicates that pulmonary vaccination may confer superior protective immunity against *Mtb* by stimulating tissue-resident memory (TRM) CD4<sup>+</sup> T cells in the lungs. The chemokine receptor CXCR3 is considered important for T cell entry to the lungs, but the requirement of CXCR3 for the development and retention of TRM is unknown. The recombinant influenza A virus (rIAV) vaccine, PR8.p25, that expresses the *Mtb* CD4<sup>+</sup> T cell epitope p25, stimulates protection against *Mtb* infection in the lung. Pulmonary delivery of the vaccine induced CXCR3 expression on p25 antigen-specific CD4<sup>+</sup> T cells that were recruited to the lungs, and at 6 weeks, a higher proportion of lung antigen-specific CD4<sup>+</sup> TRM expressed CXCR3 than total CD4<sup>+</sup> T cells.

However, CXCR3 was not required for the recruitment of CD4<sup>+</sup> T cells, as CXCR3<sup>-/-</sup> mice showed equivalent antigen-specific CD4<sup>+</sup> T cell responses in the lungs to WT mice following rIAV-PR8.p25. Surprisingly, CXCR3-deficient mice retained more p25-specific CD4<sup>+</sup> TRM in the lungs than WT mice at 6 weeks.

When CXCR3-deficient and WT P25 CD4<sup>+</sup> T cells were co-transferred into mice prior to PR8.p25 immunization, the initial recruitment of p25-specific T cells into the lungs was independent of CXCR3, but by 6 weeks, the number of CXCR3-deficient CD4<sup>+</sup> T cells was significantly reduced compared to WT T cells, and CXCR3<sup>-/-</sup> TRM were markedly reduced.

Therefore, although CXCR3 expression provided a competitive advantage for the induction of CD4<sup>+</sup> TRM in the lungs, this was not essential for CD4<sup>+</sup> T cell recruitment or the retention of CD4<sup>+</sup> TRM in the lungs following this pulmonary TB vaccine.

### EP-TBS-31 Benefit of Quantiferon-TB Gold plus in incidence of TB disease in Health care workers of Central Chest Institute of Thailand

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Environment control (minimum of 12 air change per hour (ACH) was one of the recommendation to prevent transmission of M.tuberculosis. This study would like to detect benefit of environment control by using calculate ACH model to prevent transmission of TB organism in Health care workers.

High risk health care worker group defined by who work in the frequent TB contacted area e.g. Chest clinic, TB clinic, Bronchoscopy unit, respiratory IPD, RCU, and et.al. 659 of 1351 Health care workers of Central Chest Institute of Thailand were enrolled between July 2019- June 2020.

Health care workers were separate to 3 groups: 257, 55 and 347 health care workers were in high risk group who work in the area which completely develop  $\geq 12$  air change model, high risk group under develop air change model area and low risk group, respectively. QuantiFERON-TB Gold Plus was performed to detect LTBI. 87(13.2%) Health care workers were positive IGRA. There were 4 of 87 positive IGRA participants (4.5%) develop TB disease.

All TB disease participants were negative smear and culture. 1 of 572 (0.1%) negative IGRA participants developed TB disease. 38 of 257 (14.7%) health care workers who high risk and completely develop model, 13 of 55 (23.6%) who high risk and under develop and 36 of 347 (10.3%) who low risk were positive IGRA. Risk Ratio with adjusted confounder was 0.99 (95% CI= 0.66-1.50),  $p=0.96$  and 1.36 (95% CI=0.59-3.11),  $p=0.45$  compared between high risk with completely develop and low risk, high risk with under develop and low risk.

There was benefit of air change model development more than 12 ACH to prevent TB infection in area of airborne transmission especially TB infection.

Latent tuberculosis infection rate in the high risk area with completely develop air change model is nearly equal to low risk area.

### EP-TBS-32 The blood monocyte/lymphocyte, neutrophil/lymphocyte and platelet/lymphocyte ratios in children with pulmonary tuberculosis

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More than one million children develop tuberculosis every year. Monocyte/lymphocyte, neutrophil/lymphocyte, platelet/lymphocyte ratios are simple indicators that are used to predict various diseases, but it has not yet been investigated in children with pulmonary tuberculosis.

The purpose of this study was studying the monocyte/lymphocyte, neutrophil/lymphocyte and platelet/lymphocyte ratios in children with pulmonary tuberculosis. The study was conducted in a group of 43 children with pulmonary tuberculosis. The following criteria were considered in the analysis: tuberculosis verified by the bacteriological method and/or radiological method, patient age between 6–18 years. All children were successfully cured of tuberculosis. The blood cell counts in children were studied before the start of treatment and after the end of treatment. The ratios of monocyte/lymphocyte, neutrophil/lymphocyte and platelet/lymphocyte were calculated. Comparison of the ratios before the start of treatment and after the end of treatment was carried out by calculating the Student's criterion.

The analyzed group included 19 boys (44.2%) and 24 girls (55.8%). The average age of children was  $15.0 \pm 3.3$  years.

As a result of successful treatment, the monocyte/lymphocyte ratio decreased in children. Before treatment, the ratio was  $0.26 \pm 0.17$ . After the end of treatment, in children cured of tuberculosis, the ratio was  $0.18 \pm 0.12$ . The difference is significant  $P < 0.05$ .

Similar changes were observed of the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio. These ratios decreased in children with successful treatment of tuberculosis. The neutrophil/lymphocyte ratio decreased from  $2.03 \pm 1.28$  to  $1.19 \pm 0.54$ . The difference is significant  $P < 0.001$ . The platelet/lymphocyte ratio decreased from  $12.18 \pm 11.35$  to  $6.70 \pm 2.86$ . The difference is significant  $P < 0.01$ .

In our study, we found a decrease of the blood monocyte/lymphocyte, neutrophil/lymphocyte and platelet/lymphocyte ratios in children age between 6–18 years with successful tuberculosis treatment. The ratios can be used as indicators of treatment response in children with pulmonary tuberculosis.

### EP-TBS-33 Pulmonary tuberculosis patients have an anaerobe-enriched microbiota associated with a pro-inflammatory peripheral host immune phenotype

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**Background:** The interaction between tuberculosis (TB), the leading infectious cause of death worldwide, and the human microbiome, which is critical for health, is poorly understood.

**Methods:** We characterised oral wash, induced sputum, and stool microbiota in adults with presumptive active TB [58 confirmed cases, 47 symptomatic controls (SCs)] before treatment, as well as close contacts of cases (CCCs, n=73) and close contacts of SCs (CCSCs, n=82) without active TB. Whole blood for host transcriptional profiling was consecutively collected from a subset (38 cases, 30 SCs).

**Results:** Cases and SCs had similar  $\alpha$ - and  $\beta$ -diversities and few taxonomic differences (*Paludibacter*-, *Lautropia*-, *Alloicoccus*-enriched) in oral washes and sputum. However, marked differences occurred in stool (PERMANOVA  $p=0.035$ ) with cases enriched in anaerobes (*Anaerostipes*, *Blautia*, *Erysipelotrichaceae*) and predicted amino acid and carbohydrate metabolic pathways. In pairwise comparisons with their CCCs, cases had *Megasphaera*-enriched oral and sputum microbiota and *Bifidobacterium*-, *Roseburia*-, and *Dorea*-depleted stools. Compared to their CCSCs, SCs had reduced  $\alpha$ -diversities in oral washes ( $p=0.010$ ), sputum ( $p=0.006$ ) and stool ( $p=0.006$ ) and many differential taxa. Cases differed transcriptionally from SCs (PERMANOVA  $p=0.001$ ), and co-occurrence network analysis showed that certain gut anaerobic taxa enriched in cases correlated with distinct inflammation-modulating pathways (*Blautia* and *Erysipelotrichaceae* co-occur, and correlate with death receptor signalling and EIF2 signalling pathways; *Anaerostipes* correlates with interferon signalling, Nur77 signalling in T lymphocytes and inflammasome pathways).

**Conclusion:** TB-specific microbiome relationships were identified in oral washes, induced sputum and stool collected from cases at pre-treatment. In the gut, enriched anaerobes (with likely enhanced functional capacity for short chain fatty acid production) correlate with pro-inflammatory host immune pathways known to be associated with TB disease severity and may thus modulate *Mycobacterium tuberculosis* pathogenesis via the gut-lung axis.

### EP-TBS-34 The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on rifampicin resistant and multidrug resistant tuberculosis in India and China

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**Background:** Despite recent advances, how new tuberculosis (TB) vaccines might affect rifampicin resistant and multidrug resistant TB (RR/MDR-TB) is unknown. We investigated the epidemiologic impact and cost-effectiveness of hypothetical prevention of disease TB vaccines on RR/MDR-TB in India and China.

**Methods:** We constructed a dynamic, drug-resistance-stratified Mycobacterium tuberculosis transmission model. We introduced novel vaccines from 2027, with post- (PSI) or pre- and post- infection (P&PI) efficacy, conferring 50% efficacy for 10 years, routinely 9-year olds and 10-yearly to ages  $\geq 10$ . We estimated percent RR/MDR-TB incidence rate reduction in 2050 and vaccine cost-effectiveness over 2027–2050. We considered three cost-effectiveness thresholds (one gross domestic product (GDP) per capita, and two healthcare opportunity cost based (HCO)).

**Results:** By 2050, P&PI vaccine reduced RR/MDR-TB incidence rate by 72% (uncertainty interval: 65–77) and 73% (UI: 66–76), and PSI vaccine by 47% (UI: 37–58) and 29% (UI: 27–31) in India and China, respectively. In India, we found P&PI and PSI vaccines priced at US\$10 cost-effective at all three thresholds. In China, both vaccines were cost-effective at the 1-times GDP and upper HCO thresholds with  $\geq 72\%$  probability. The P&PI vaccine was predicted to avert 0.8 (UI: 0.5–1.4) million and 1.0 (UI: 0.6–1.3) million RR/MDR-TB treatments over 2027–50, in India and China, respectively.

**Conclusions:** New TB vaccines are likely to substantially reduce future burden of RR/MDR-TB, while averting need for RR/MDR-TB treatment. Vaccination may be cost-effective depending on vaccine characteristics and setting.

### EP-TBS-36 Novel, culture-free, same-day TB diagnosis with ultrasensitive ELISA

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**Background:** NAATs are now widely used for TB diagnosis, but they cannot discriminate live bacilli from dead ones. A time-consuming culture test is still considered as a gold standard that can detect only live bacilli. In the present study, we propose a *de novo* TB diagnosis method for the detection of only live bacilli that has the same high-detection sensitivity as a culture test and can be performed within 5 hours.

**Materials/methods:** TB patient sputum was pretreated with protease, and the specimen was heated at 46°C for 1 hour to induce the secretion of specific protein, MPT64, from only live *M. tuberculosis*. This protein was detected with our new ultrasensitive diagnosis method that was based on ELISA coupled with thio-NAD cycling. We compared our results with those of a culture test (MGIT), a smear test (Kinyoun staining) and a NAAT (Xpert).

**Results:** The limit of detection for MPT64 in our ultrasensitive ELISA was 0.2 attomoles/assay. Using the cutoff value of the measuring absorbance at 17 mAbs, which corresponded to *ca.* 330 CFU/mL in a culture method, the sensitivity was 86.9% (93/107, 95% CI: 79.0 - 92.7%), and the specificity was 92.0% (770/837, 95% CI: 89.9 - 93.7%) compared to that of MGIT. These were better than those obtained from Kinyoun staining tests and were not significantly different from those of Xpert tests. Further, the validity for drug effectiveness examination was shown by our ultrasensitive ELISA tests better than by Xpert tests because our tests detected only live bacilli.

**Conclusions:** A novel, culture-free, same-day TB diagnosis method detects only live *M. tuberculosis* with a high-detection sensitivity. This method is especially useful for the patients under TB-treatment to evaluate whether it is effective or not.

### EP-TBS-37 Tuberculosis screening in point-of-care settings: proof-of-concept for a fast and easy sample-to-answer qPCR-based protocol

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We sought to develop a low cost sample preparation and DNA extraction protocol to overcome some of the existing hurdles in tuberculosis (TB) diagnostic in point-of-care (POC) settings. Several solutions were evaluated to liquefy a mucin-based matrix, supplemented with either *M. tuberculosis* H37Rv strain DNA or intact cells. The mixture was aliquoted onto filter papers embedded with solubilizing agents. Most of the nucleic acids present in the mixture then binds to the paper.

Different protocols were evaluated to elute the DNA from the paper, using a portable qPCR instrument to detect the insertion sequence IS6110. The limit of detection (LOD) of the best protocol was determined using parallel seeding and colony counting. The protocol was also evaluated using seventeen sputum samples previously characterized by GeneXpert or culture, in two instruments (ABI7500 or the portable Q3-Plus) and two reagents storage formats (frozen or ready-to-use).

Solutions containing guanidine isothiocyanate exerted the best liquefying effect on the mucin-based matrix. DNA was eluted from one 6-mm filter paper punch briefly incubated at 95 °C. The resulting DNA contained impurities, which were eliminated by a simple 1:10 dilution.

The described protocol presents an apparent LOD of 2 CFU/mL. Challenging the protocol with previously characterized samples showed substantial agreement with GeneXpert results (sensitivity 90%, agreement 88.9%, kappa coefficient 0.77), and moderate agreement with culture results (sensitivity 100%, agreement 78.9%, kappa coefficient 0.58).

This work presents a sensitive proof-of-concept protocol for sputum liquefaction and decontamination followed by a straightforward DNA extraction procedure streamlined with a ready-to-use qPCR in a portable instrument, which can easily be adapted to differentiate dead and alive bacilli. The proposed procedure is a simple protocol with a small number of steps as well as minimal use of reagents and equipment, resulting in an easy-to-use tool for MTB screening in POC settings.

## EP-TBS-38 Diagnostic accuracy of three urine lipoarabinomannan tuberculosis assays in HIV-negative outpatients

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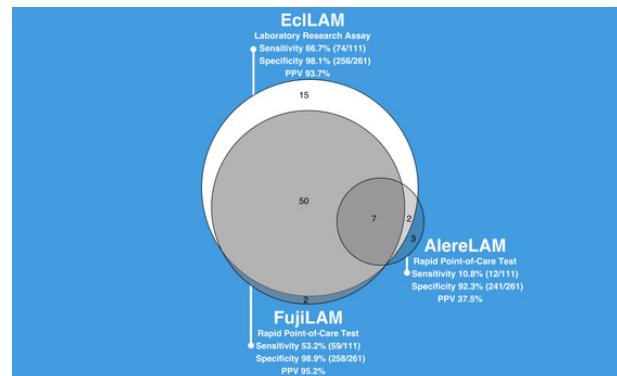
**Background:** Inadequate tuberculosis (TB) diagnostics are a major hurdle in the reduction of disease burden. Lipoarabinomannan (LAM) in urine is a promising TB diagnostic biomarker. The novel Fujifilm SILVAMP TB LAM (FujiLAM) point-of-care test previously showed improved sensitivity in PLHIV compared to AlereLAM. Here, we assessed the diagnostic accuracy of FujiLAM, AlereLAM and a laboratory-based ultrasensitive electrochemiluminescence LAM (EclLAM) research assay for TB diagnosis in HIV-negative outpatients.

**Methods:** In this multicentre diagnostic test accuracy study, we recruited HIV-negative adults with symptoms suggestive of pulmonary TB presenting to outpatient healthcare centres in Peru and South Africa. Urine samples were tested using FujiLAM, AlereLAM and EclLAM. The primary objective was to estimate and compare the diagnostic accuracy of the three LAM tests against microbiological and composite reference standards.

**Results:** Between February 9, and October 4, 2017, we enrolled 372 HIV-negative participants in the study. The prevalence of microbiologically confirmed TB was 30%. Compared to the microbiological reference standard, the sensitivities of AlereLAM, FujiLAM and EclLAM were 10.8% (95% CI 6.3to18.0), 53.2% (43.9to62.1), and 66.7% (57.5to74.7) respectively. The specificities of AlereLAM, FujiLAM and EclLAM were 92.3% (88.5to95.0), 98.9% (96.7to99.6), and 98.1% (95.6to99.2) respectively. Positive Likelihood Ratio of AlereLAM, FujiLAM and EclLAM were 1.4, 46.2, and 34.8 and positive predictive values 37.5%, 95.2%, and 93.7% respectively.

**Conclusion:** Compared to AlereLAM, FujiLAM detected five times more TB patients in HIV-negative participants, has a high positive predictive value and has the potential to rule-in TB in broad populations at the point-of-care. EclLAM demonstrated that additional sensitivity gains are possible, which highlights LAM's potential as a TB diagnostic biomarker. Additional

studies are required to assess the performance of new LAM tests in prospective cohorts using fresh samples, their cost-effectiveness, user-friendliness and patient impact in real-world clinical settings.



[Figure. Diagnostic accuracy of three urine lipoarabinomannan (LAM) tuberculosis assays in HIV-negative outpatients]

## EP-TBS-39 To study the presence of live Mycobacterium tuberculosis in resected lung specimens of patients undergoing lung resection surgery for post-tuberculosis sequelae

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**Introduction:** Post-tuberculosis sequelae like bronchiectasis, destroyed lung and aspergilloma generally occur in cavitary tuberculosis. It is unclear whether patients who develop haemoptysis, harbour active mycobacterium beyond parenchymal destruction caused by tuberculosis. Several published studies have demonstrated presence of active TB bacilli in multi drug resistant cavities. However, microbiological evaluation for presence of live bacilli in patients with sequelae has not been done since 1964.

**Methods:** We performed pilot study July 2017- December 2018 on patients who underwent resection for post tuberculosis sequelae. After, confirmation of absence of clinical evidence of tuberculosis, samples were collected from the diseased sections of the lung, normal appearing lung as well as resected bronchus margin and cultured for the presence of Mycobacterium tuberculosis

**Results:** Of the 46 patients enrolled, mean age was 33 with 54% male and 46% female patients. 87% presented with haemoptysis and 13% septic symptoms. 48% patients had fungal ball as the post TB sequelae, 41% bronchiectasis and 11% destroyed lung. The number of courses of anti-tubercular therapy taken by patients varied from 1-6 and 37% patients took more than one course. The lag period for symptom development after treatment completion of pulmonary tuberculosis was 5 years and lag period to surgery was 9 years (1-31 years).

None of the resected specimens revealed presence of live bacilli both by MGIT and Lowenstein-Jensen medium for culture. Smear positive status in 35% diseased sections, 20% normal appearing sections or 26% bronchial margin may be suggestive of dead bacilli. 10 specimens (22%) had granulomatous inflammation on histopathology with 5 AFB smear positivity on histopathology.

**Conclusions:** Patients who complete current standard therapy for pulmonary tuberculosis and subsequently present with sequelae are unlikely to harbor active disease. While surgery is indicated for symptomatic sequelae there is possibly no role of adjuvant anti-tubercular therapy.

### EP-TBS-40 What can tuberculosis prevalence surveys tell us about the duration of asymptomatic bacteriologically-positive disease?

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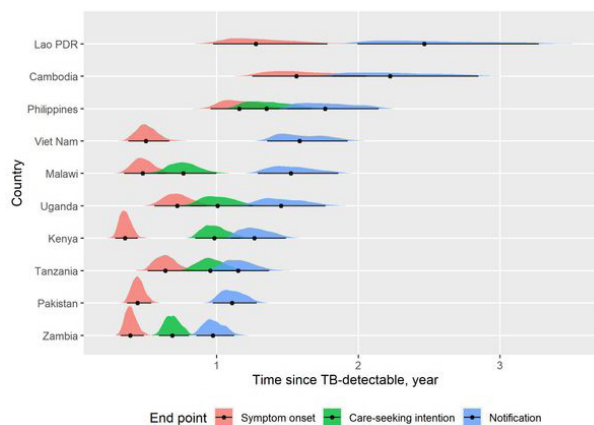
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**Background:** Ratios of tuberculosis prevalence to notification rates are used to characterise the typical durations of tuberculosis disease. However, standard approaches ignore the spectrum of tuberculosis disease, and time with few or no symptoms prior to care-seeking.

**Methods:** We developed novel analytical models to estimate progression from initial bacteriological-positivity including (depending on data): smear conversion, symptom onset and initial care-seeking. Case-detection ratios were also estimated by fitting the model to tuberculosis prevalence and notification data (1 subnational and 10 national datasets) within a Bayesian framework using Markov chain Monte Carlo methods.

**Results:** For Kenya and Blantyre, Malawi individual-level data were available. The sex-specific durations of asymptomatic bacteriologically-positive tuberculosis were 0.31 years (95% Credible Interval, CrI: 0.21-0.45) and 0.41 years (95% CrI: 0.29-0.54) for females and males in Kenya; 0.28 years (95% CrI: 0.13-0.51) years and 0.22 years (95% CrI: 0.097-0.41) in Blantyre. Age-stratified analysis of data for Kenya showed no strong age-dependence in durations. For Blantyre, HIV-stratified analysis estimated an asymptomatic duration of 0.13 years (95% CrI: 0.059-0.27) for HIV-positive people, shorter than the 0.46 years (95% CrI: 0.23-0.79) for HIV-negative people. Additionally, fewer cases went unnotified among HIV-positive than HIV-negative people (7% vs 29%). Analysis across 10 national datasets found asymptomatic

tuberculosis durations in the range 0.3 - 0.7 years for African countries; three countries in Asia (Cambodia, Lao PDR, and Philippines) showed longer durations of  $\geq$  1 year. For the six countries with relevant data, care-seeking typically began half-way between symptom onset and notification.



[Figure.]

**Conclusion:** Asymptomatic TB disease typically lasts around 6 months. We found no evidence of age-dependence, but much shorter durations among people living with HIV, and longer durations in some Asian settings. Time seeking care or with recognised symptoms still accounts for around half disease of duration.

### EP-TBS-41 An RNA signature for tuberculosis risk in pregnant women: a prospective cohort study from India

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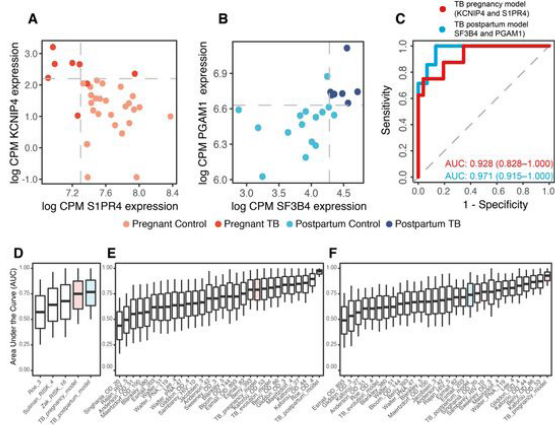
**Background:** Identifying high-risk patients for developing active TB is a priority. In women, this occurs postpartum but transcriptional TB studies have excluded pregnant women. We identified differentially expressed genes (DEGs) in pregnant women who did and did not progress to active TB.

**Methods:** We conducted a prospective study of pregnant women with latent TB in India, collecting blood for transcriptional analysis at study entry, 6 weeks postpartum and TB diagnosis. We matched 10 women with active TB postpartum to 10 controls by HIV status and gestational age. We compared cases and controls at entry (pre-TB) and postpartum (TB vs. no TB). We used



machine-learning analysis and count gene expression matrix to identify DEGs for cases and controls. Significance was defined as FDR-adjusted  $p < 0.05$  and fold change  $> \pm 1.4$ .

**Results:** We applied Random Forest algorithm to identify the most informative gene set to classify samples within groups (Figure). Expression of  $KCNIP4 > 2.2$  log CPM and  $S1PR4 < 7.3$  log CPM indicated a high probability of developing active TB postpartum.  $SF3B4 (>4.3$  log CPM) and  $PGAM1 (>6.6$  log CPM) correctly classified postpartum women with and without active TB. Both pairs displayed elevated accuracy (AUC  $> 0.9$ ) and were unique from 36 published TB signatures. Molecular degree of perturbation (MDP) scores assessed variation of gene expression. Pregnant women who developed active TB had a higher MDP than those who did not. Controls had a lower MDP postpartum than during pregnancy, whereas women with active TB had a higher MDP postpartum.



**Figure:** Dot plots from the log CPM values of the Machine Learn model genes in the (A) TB pregnancy comparison and (B) postpartum TB comparison. (C) ROC of the Machine Learn model genes (Random Forest). Barplot of AUC values from all signatures, the DEGs and decision tree gene set for (D) TB pregnancy (pre-TB) and TB postpartum; (E) postpartum cases

**Conclusions:** We identified 2 genes that prospectively differentiated pregnant women who developed active TB postpartum from those who did not. Moreover, these genes were not identified in previous TB signatures. These findings need to be confirmed in other cohorts of pregnant women, but could be useful in targeted TB prevention programs.

## EP-TBS-42 Analysis of mycobacterial trans-renal DNA for the diagnosis of Tuberculous Meningitis in adults

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Tuberculous Meningitis (TBM) is associated with a high mortality and morbidity in developing countries and its diagnosis is limited due to inadequate accuracy of existing tests. In this study we assessed the utility of detecting trans-renal mycobacterial DNA (Tr-MTB DNA) in urine samples for TBM diagnosis. We also endeavored to assess the source of this Tr-MTB DNA.

Firstly, a pilot study was performed, wherein urinary extra-cellular vesicles (EVs) were isolated from TBM and non-TBM samples. The presence of urinary exosomes and micro-vesicles was confirmed by immunoblotting and scanning electron microscopy.

Further, we successfully isolated Tr-MTB DNA from the EV-fraction (EV-DNA) and EV-free fraction (EV-free DNA). We developed a 'Tr-MTB DNA' assay to detect a highly repetitive 36-bp fragment of *Mycobacterium tuberculosis* and used EV-DNA and EV-free DNA for assay development. The developed assay could successfully identify Tr-MTB DNA in either the EV and/or EV-free portion. The developed assay was applied in a blinded study on suspected TBM (n=37) and Non-TBM samples (n=10). The suspected TBM samples were categorized in 'Definite TBM' (n=8), 'Probable TBM' (n=15), 'Possible TBM' (n=14) category according to the composite reference standard developed by Marais et al., 2010. The sensitivity of the 'Tr-MTB DNA' assay in EV-fraction was 95.6% (95% CI: 78.05%-99.89%) with 100% (95% CI: 69.15%-100%) specificity, whereas the sensitivity of the assay in EV-free fraction was 82.6% (95% CI: 69.15%-95.05%) with the same specificity. In combination, the sensitivity and specificity of Tr-MTB DNA (EV-DNA + EV-free DNA) was 100%. Together, these findings confirmed that one of the sources of 'Tr-MTB DNA' as extra-cellular vesicles and that these vesicles play some role in the pathological physiology of TBM. The assay estimates exceed the Target-product-profile defined by WHO, and shows promise to be evaluated in larger studies to accurately assess its utility for TBM diagnosis.

### EP-TBS-43 Developing a tool to identify and screen Latent Tuberculosis Infection (LTBI) with likelihood of progression to active Tuberculosis (ATB)

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Tuberculosis (TB), an infection caused by the bacterium *Mycobacterium tuberculosis* (MTB), is the world's number one cause of death from an infectious disease. A quarter to third of the human population is believed to be infected, with about 10 million active cases and 1.6 million deaths each year, mostly occurring in Asia and Africa. The huge global economic burden caused by MTB infection is due to lost productivity, the expense of prolonged treatment, and the emergence of drug-resistant TB (DRTB). Most TB infections are asymptomatic, or latent (LTBI), but about 10% of LTBI cases become active (ATB) within three years, with significant mortality. Global effort to eradicate TB has shifted the emphasis to identifying and proactively treating those with LTBI.

Next Generation Sequencing (NGS), has led to the availability of genomic and transcriptomic data associated with a wide range of diseases. Interrogation of RNA-Seq data from LTBI and ATB patients has yielded unique transcripts that may be used to develop highly sensitive screening tools.

We propose to analyze existing RNA-Seq and microarray data from TB patients to identify isoforms that would allow for finding biomarkers unique to LTBI. Additionally, we propose to find biomarkers, which would identify subjects with LTBI likely to progress to ATB disease.

We have identified 367 high quality RNA-Seq datasets available publicly on Gene Expression Omnibus (GEO) derived from Healthy, LTBI, and ATB subjects. Using a custom built computational pipeline, our analysis found 21 known and novel splice junctions, which stratify LTBI from healthy subjects. Additionally, we have analyzed RNA-Seq data derived from whole blood obtained from 14 LTBI donors longitudinally over two years who went on to develop ATB. Comparing these LTBI subjects to those who did not develop ATB, we have found 68 splice junctions, which are differentially expressed.

### EP-TBS-44 QuantiFERON TB plus-negative results in clinically diagnosed paediatric tuberculosis: immune suppression or misdiagnosis?

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Interferon gamma release assays (IGRAs) measure interferon gamma (IFN- $\gamma$ ) released by effector T-cells when blood of individuals with prior exposure to *Mycobacterium tuberculosis* (MTB), is stimulated with MTB-specific antigens. This memory response is known to linger even after treatment. QuantiFERON TB (QFT)- plus, is an IGRA that is optimized with innovative MTB-specific antigens that elicits both CD4 + and CD8+ T-cell responses. QFT-plus is reported to perform as well in children under five years old or with HIV coinfection as in adults.

We evaluated the QFT-plus performance in 73 Ghanaian children at three phases (baseline, intensive phase, and treatment completion) of TB treatment in two specialist hospitals in Accra, Ghana. Diagnosis of paediatric TB for all the children was based only on clinical and radiologic findings. QFT-Plus positivity was 45% (18/40) among children at baseline (before initiation of TB treatment), 35% (6/17) at intensive phase (month 2 of TB treatment), and 50% (8/16) at treatment completion. Indeterminate results (10/73) were all due to very low (<1.0 IU IFN- $\gamma$ /ml) mitogen responses. QFT positivity was not affected by type of TB (pulmonary or extrapulmonary), age, or HIV status.

Median IFN- $\gamma$  values in response to MTB antigens were significantly higher in the baseline group compared to the intensive phase group (TB1 median 7.5 versus 0.02 IU IFN- $\gamma$ /ml, TB2 median 6.92 versus 0.05 IU IFN- $\gamma$ /ml; P=0.0005) and treatment completion group (TB1 median 7.5 versus 0.05 IU IFN- $\gamma$ /ml, TB2 median, 6.92 versus 0.06 IU IFN- $\gamma$ /ml; P<0.005). Median mitogen values were not significantly different among the three groups.

In summary, the study provides baseline data to support inclusion of QFT-plus in a diagnostic algorithm for TB in children. However, the overall low QFT positivity of 43.8% (32/73) across the different phases of treatment raises concern about immune suppression or misdiagnosis in the absence of microbiological confirmation.

### EP-TBS-45 Evaluation of a blood-based antigen test for tuberculosis in HIV-exposed children younger than 5 years

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Non-sputum methods are urgently needed to improve tuberculosis (TB) diagnosis and treatment monitoring in children. We evaluated the diagnostic accuracy of a blood-based assay, which detects and quantifies a TB-specific CFP-10 peptide for TB diagnosis, in HIV-exposed children <5 years old from a multicenter TB prevention trial conducted in southern Africa (IMPAACT P1041).

Cryopreserved sera from 519 HIV-exposed children (284 HIV-infected, 235 HIV-uninfected) were evaluated for CFP-10 peptide expression. BCG-immunized, TB-disease-negative children aged 91-120 days were randomized to isoniazid or placebo and followed for up to 192 weeks for TB infection and disease.

For this analysis, children were classified as Confirmed, Unconfirmed, or Unlikely TB cases using 2015 NIH Pediatric TB diagnostic criteria based on clinical, laboratory, histopathological, and radiological evaluations.

In HIV-infected children, serum CFP-10 signal had 100% sensitivity for Confirmed TB (5/5, 95% confidence interval [CI], 47.8–100) and 83.7% sensitivity for Unconfirmed TB cases (36/43, 95% CI 69.3–93.2), with 93.1% (203/218, 95% CI 88.9–96.1) specificity.

In HIV-uninfected children, serum CFP-10-positivity detected the single Confirmed TB case and 75.0% of Unconfirmed TB cases (15/20; 95% CI 50.9–91.3), with 96.2% (177/184, 95% CI, 92.3–98.5) specificity. CFP-10 peptide signal was detected in serum up to 60 weeks before TB diagnosis, and its positivity and concentration declined following anti-TB therapy initiation.

These capabilities address important clinical needs, and warrant further investigation to validate these findings and address the utility of similar blood-based biomarker diagnostics for these clinical applications.

### EP-TBS-46 Adverse drug reactions in MDR TB patients on ATT

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**Introduction:** The purpose of this study is to describe the common adverse effects of anti-tubercular therapy (ATT) in patients with primary MDR tuberculosis. Early recognition of these common adverse effects and their prompt treatment may lead to better adherence to ATT and improve the overall prognosis.

**Methodology:** This observational study was conducted to describe the side effects of anti-tubercular therapy in patients with MDR-TB. 100 patients diagnosed with MDR-TB and taking anti-tubercular therapy were included in the study. Adverse drug reactions were determined based on the clinical presentation and a patient questionnaire.

Baseline investigations including blood sugar levels, CBC, LFT, RFT, ECG were done in all the patients.

#### Inclusion criteria:

Patients more than 25 years of age  
Patients diagnosed with primary MDR-TB  
Patients shorter MDR-TB regimen  
Patients taking anti-tubercular therapy

#### Exclusion criteria:

Patients not consenting for the study  
Patients with recent episode of myocardial infarction (in past 2 months)  
Patients with recent episode of stroke (in past 2 months)

**Results:** In our study 80% were male and 20% were female

24% of patients were on shorter MDR-TB regimen

Most common age group was 35-40 years of age

Gastritis was the most common side-effect observed in 80% of the patients with 1st week of starting the treatment

Hepatitis was observed in 30% patients

Itching and severe dermatitis was observed in 10% patients

Peripheral neuropathy was observed in 5% patients

Hypothyroidism was observed in 1-2% patients

Blurring of visions was observed in 1-2% of patients

Arrhythmia was observed in 1-2% of patients

**Conclusions:** Early treatment of these common adverse effects of ATT would lead to better adherence to treatment and reduce the incidence of defaulters and XDR-TB.

### EP-TBS-47 Species and drug susceptibility profile of non-tuberculous mycobacteria isolated from presumptive TB cases

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**Background:** This study aims to identify the pulmonary NTM isolated from presumptive TB cases and to determine the drug susceptibility patterns (DST) of the isolated species. We used Sensititre plate testing method for the first time to determine its utility in DST of NTM.

**Method:** A prospective cohort of adults with respiratory symptoms and high suspicion of pulmonary NTM disease were referred to the ICMR-National Institute for Research in Tuberculosis, Chennai during 2017 – 2020. Three consecutive sputum samples were collected for smear and culture of acid-fast bacilli. Culture isolates were speciated using Genotype CM/AS kit and were subjected to drug susceptibility testing (DST) using Sensititre SLOWMYCO system and interpreted using CLSIM24 guidelines.

**Results:** The NTM species identified were *M. kansasii* (22), *M. intracellulare* (13), *M. avium*, *M. simiae*, *M. malmoense*, *M. kyorinense*, and *M. gordonae* (one each). Two mixed cultures were identified (*M. gordonae* & *M. avium* and *M. intracellulare* & *M. fortuitum*). Till date, Sensititre DST has been performed for 9 strains of *M. avium-intracellulare* complex (MAC) and 8 strains of *M. kansasii*.

While the *M. avium* strain was resistant to clarithromycin, the *M. intracellulare* isolates were sensitive. The MAC strains were susceptible to most of the antibiotics, except for two strains of *M. intracellulare* which were resistant to Linezolid. Out of the 8 *M. kansasii* isolates, 2 were resistant to clarithromycin, 6 were resistant to doxycycline, and one each was resistant to rifabutin and rifampicin.

**Conclusions:** The study indicates that identification of NTM in presumptive TB cases should be made as a mandate in programme for early identification of species for appropriate treatment. Use of Sensititre plate method for DST of NTM improves our ability to detect antibiotic sensitivity patterns. However expanded MICs for all the antibiotics in use should be considered by CLSI to give results for low-level resistance detection.

#### EP-TBS-48 MAMA-PCR assay for the detection of point mutations associated with drug resistance in *Mycobacterium tuberculosis* clinical isolates

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Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* complex, being a worldwide health problem. In 2018, the incidence rate of TB in Baja California, México, was 58.3 cases per 100,000 inhabitants, reporting as the state with the highest incidence of pulmonary TB in the country.

We used the MAMA-PCR technique, designing primers based on the most frequent resistance mutations identified in clinical isolates of *M. tuberculosis* from patients from Baja California, México. Seven pairs of primers were standardized, four of them for mutations in genes associated with first-line drugs; *rpoB* (RIF) H526T, *katG* (INH) S315T, *embB* (EMB) Q497R and *pncA* (PZA) V180G and three of them for second-line drug mutations; *rpsL* (SM) K43R, *eis* (AMK) P114S and *gyrA* (FQ) S91P.

The technique was applied in clinical isolates from patients with pulmonary TB, allowing allelic discrimination of wild and mutant isolates. A total of 35 drug-resistant *M. tuberculosis* isolates in Baja California were analyzed by this assay, resulting in 94.3% sensitivity

(32 of 35) and 88.6% concordance (31 of 35) relative to DNA sequencing. The results suggest that the MAMA-PCR assay is rapid and straightforward to use and could be performed for the detection of drug resistance in *M. tuberculosis* to counterpart conventional culture-based assays.

Likewise, the method, together with the primers designed in this study, was performed on the Mini-PCR® portable equipment and the Bluegel® electrophoresis chamber, allowing *M. tuberculosis*'s molecular identification and the drug resistance profile in isolates and clinical samples of *M. tuberculosis*.

The use of portable equipment enables the technique to be within reach of health centers far from state hospitals and laboratories. Therefore, it is closer to patients, thus allowing the development of Point of Diagnostic Care (Point-of-Care Diagnostics).

#### EP-TBS-49 Genomic diversity in *Mycobacterium tuberculosis* from human lung resections reveals a high degree of multiclonal infections in a high-burden MDR-TB setting

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Multiclonal infections occur when at least two unrelated strains of the same pathogen can be detected in an individual. This has been linked to worse clinical outcomes in tuberculosis infections, as undetected strains presenting different antibiotic resistance profiles can lead to treatment failure.

Also, TB vaccine development strongly depends on the capacity of a vaccine to mount a proper immune response to avoid infection with a virulent strain, a context in which estimating the frequency of multiclonal infections is invaluable.

Here, we present a study of the extent of multiclonal infections in Georgia, including sputum and surgical resections. Access to lung samples enhanced the detection of multiple strains as opposed to just using a clinical sputum sample, identifying a significant number of multiclonal infections with complex scenarios.

We also characterized bacterial diversity finding different patterns across patients, and highlighting the importance of ROS as a selective pressure acting along treatment.

Our results suggest that the magnitude of multiclonal infections in high-burden settings is likely to be underestimated when only using sputum samples. They also have implications on clinical outcomes and to understand the impact of candidate vaccines.

### EP-TBS-50 Pathogen genome sequencing to guide treatment regimen designs for multidrug-resistant tuberculosis

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**Rationale:** Comprehensive and reliable drug susceptibility testing (DST) is urgently needed to provide adequate treatment regimens for patients with multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB).

**Objectives:** We investigated if next generation sequencing (NGS)-based predictions of drug susceptibility of *Mycobacterium tuberculosis*-complex isolates from patients with MDR/RR-TB can guide the design of effective MDR/RR-TB treatment regimens.

**Methods:** NGS-based genomic DST predictions were compared with phenotypic DST results by *Mycobacteria* growth indicator tubes (MGIT) for *M. tuberculosis*-complex isolates from MDR/RR-TB patients admitted to a TB reference center in Germany between 01/01/2015 and 04/30/2019. Standardized treatment algorithms were applied to design individualized therapies based on either genomic or phenotypic DST results, and discrepancies were further evaluated by determination of minimum inhibitory drug concentrations (MIC) using Sensititre MYCOTBI and UKMYC microtiter plates.

**Measurements and main results:** In 70 patients with MDR/RR-TB, agreement among 1048 pairwise comparisons of genomic and phenotypic DST was 86.3%; 76 (7.3%) results were discordant, and 68 (6.5%) could not be evaluated due to presence of mutations with yet unknown implications for drug resistance. Importantly, 549/561 (97.9%) predictions of drug susceptibility were phenotypically confirmed in MGIT, and 27/64

(42.2%) false positive results were linked to previously described mutations mediating a low or moderate MIC increase. Virtually all drugs (99.0%) used in combination therapies that were inferred from genomic DST, were confirmed to be susceptible by pDST.

**Conclusions:** NGS-based genomic DST can reliably guide the design of effective MDR/RR-TB treatment regimens.

### EP-TBS-51 An evolutionary functional genomics approach identifies novel candidate regions involved in isoniazid resistance in *Mycobacterium tuberculosis*

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Efforts to eradicate tuberculosis are hampered by the rise and spread of antibiotic resistance. Several large-scale projects have aimed to specifically link clinical mutations to resistance phenotypes, but they were limited in both their explanatory and predictive powers.

Here, we combine functional genomics and phylogenetic associations using clinical strain genomes to decipher the architecture of isoniazid resistance and search for new resistance determinants. This approach has allowed us to confirm the main target route of the antibiotic, determine the clinical relevance of redox metabolism as an isoniazid resistance mechanism and identify novel candidate genes harboring resistance mutations in strains with previously unexplained isoniazid resistance.

This approach can be useful for characterizing how the tuberculosis bacilli acquire resistance to new antibiotics and how to forestall them.

### EP-TBS-52 Antibiotic resistance profile determination using whole genome sequencing

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The WHO estimates that in 2018, 3.4% of new cases of tuberculosis cases and 18% of previously treated cases were multi-drug resistant. Additionally, 13.1 thousand extensively-drug resistant cases were confirmed by laboratory testing. The prioritization of research that allows for characterization of resistance profiles to inform drug treatment of these cases remains crucial. Here, MRI Global presents an antibiotic resistance profile determination pipeline, using whole genome sequencing, for the National Institutes of Health (NIH-DAIDS) Mycobac-

terium tuberculosis (Mtb) Quality Assessment Program (TBQA), in partnership with Johns Hopkins University (JHU). These data seek to connect genomic variants to drug resistance. We present an initial set of 10 priority isolates, selected based on phenotypic drug susceptibility testing, collection regions, and other phenotypic findings. Using gently extracted gDNA, these genomic assemblies utilize both the Oxford Nanopore MinION and the Illumina MiSeq platforms to create a genome assembly generated using long reads and short reads. Assemblies are analyzed for predicted markers of antibiotic resistance and cross referenced with existing AST data provided by JHU. This data will contribute to the body of research concerning identification of genetic elements potentially associated with resistance to specific classes of antimicrobial agents. These repository results will supplement ongoing NIH-DAIDS clinical trials by adding to the completeness and quality of the characterization data available for each isolate.

### EP-TBS-53 Rapid genomic drug resistance prediction from clinical Mycobacterium tuberculosis specimens using amplicon based deep sequencing based on Deeplex-MycTB

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Rapid, comprehensive determination of drug resistance of Mycobacterium tuberculosis complex (Mtb) isolates is essential for effective tuberculosis (TB) treatment.

We performed a pilot evaluation of the Genoscreen Deeplex<sup>®</sup>-MycTB targeted deep sequencing assay for drug resistance prediction compared to whole genome sequencing (WGS), phenotypic drug susceptibility testing (pDST), and Hain MTBDRplus and MTBDRsl line probe assays (LPA). In 81 cultured samples, Deeplex<sup>®</sup>-MycTB detected 100 resistance-mediating mutations in 18 drug resistance genes compared to 98 by WGS. Two resistance variants with 4.9%-6.8% frequencies were identified by Deeplex<sup>®</sup>-MycTB only due to deeper sequencing.

Of 50 clinical specimens, complete resistance predictions could be made for 39 (including all smear positive, five weakly positive and two negative). Concordances between Deeplex<sup>®</sup>-MycTB drug susceptibility/resistance predictions and pDST ranged from 94.9% (isoniazid) to 97.4% (rifampicin, pyrazinamide, ethambutol) on all 39 samples, and from 75% (prothionamide) to 88.9%

(fluoroquinolones) and 100% (aminoglycosides, linezolid, bedaquiline) for second-line drugs tested on 2 to 9 samples. Five of 166 (3.0%) phenotypically susceptible isolates were predicted resistant by Deeplex<sup>®</sup>-MycTB.

Three of those were minority variants (also undetected by LPA probes) that involved low resistance level mutations (to isoniazid and moxifloxacin), and two were mutations known to be associated with pDST variability to rifampicin and ethambutol. Three of 29 (10.3%) resistance phenotypes (one for isoniazid, two for prothionamide) had no matching mutation by Deeplex<sup>®</sup>-MycTB.

In conclusion, with its analytical range superior to LPAs, Deeplex<sup>®</sup>-MycTB opens a new gateway for rapid, near comprehensive TB DST from cultures or clinical specimens directly, including key drugs in new MDR-TB regimens such as bedaquiline and linezolid.

### EP-TBS-54 Multi-resistant tuberculosis and HIV infection in Kinshasa: 2011-2018. DRC "Epidemiological, clinical and therapeutic aspects"

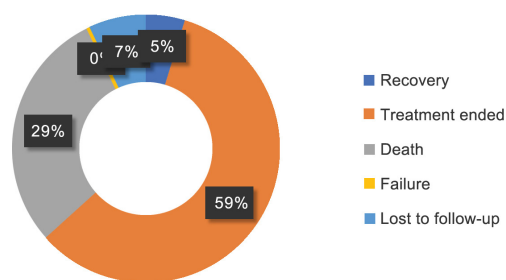
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**Context:** Tuberculosis (TB) and HIV constitute a hellish couple for the patient in countries with limited resources. TB is one of the main killers of people living with the human immunodeficiency virus (PLHIV). This situation is further amplified with the emergence of multidrug-resistant strains of tuberculosis (MDR). DRC, one of the 30 countries bearing the global burden of TB, ranks 14th in MDR-TB and 8th in TB / HIV co-infection (1); Kinshasa, is the province most affected by TB and HIV. (3), however, information on MDR-TB / HIV co-infection remains poorly documented in the country.

**Methodology:** An 8-year (2011-2018) retrospective descriptive study of MDR patients infected with HIV treated in Kinshasa conducted. the prevalence, epidemiological, clinical, and therapeutic aspects of multidrug-resistant tuberculosis co-infection were analyzed.

**Results:** A total of 1959 TBMDR patients were notified, 236 of whom were HIV positive, i.e. 12%. Of the 236 patients: women predominated 59%, sex ratio F / H1.4. The median at 38, the 15-44 age group was more affected (70%) and children accounted for 2% (5/236). 60% of patients (142/236) had suffered from TB. Pulmonary localization predominated (90%). Median time to treatment was 31 days, patients received the long and short regimen. The outcome was favorable in 64% of cases, 29% died, 7% lost to follow-up.





[Figure. Therapeutic outcome of TBMDR in Kinshasa: 2011-2018]

**Conclusion:** The HIV prevalence in MDR-TB patients is only as high in susceptible TB, women are more affected and young adults. The history of tuberculosis was present in most patients and the high case fatality 29%. Effective management measures and continuation of the determinants study may improve treatment outcomes.

**Keywords:** TBMDR / HIV co-infection, Epidemiology, Clinic, Therapeutic outcome, Kinshasa

### EP-TBS-55 Long read DNA sequencing of XDR/MDR tuberculosis samples to investigate factors leading to resistance and virulence

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DNA sequencing of the tuberculosis pathogen using “next generation” short read technology has a number of limitations including mapping and assembly issues due to repetitive regions and the inability to fully characterize structural variants.

Approximately 10% of the genes in the tuberculosis genome consist of PE/PPE family genes which are highly repetitive and thus difficult to map, assemble, and analyze using short read technology. PE/PPE family genes have been associated with both drug resistance and virulence. Structural variants have the potential to impact drug resistance and virulence but are difficult to study using short read sequencing technologies.

In addition, the standard H37Rv TB reference genome has been shown to be missing critical variants and genes related to virulence. Third generation long read sequencing technologies like PacBio address many of these issues.

The NIAID TB Portals Program is a multi-national collaboration for tuberculosis (TB) data sharing and analysis to advance TB research. The program collects extensive clinical data and biological samples from a consortium of 12 countries, with a focus on drug resistance. Fifteen samples which had been previously sequenced using short read technology were selected for PacBio long read sequencing. The samples were selected using

drug sensitivity and lineage information to identify a set of highly drug resistant samples with a diverse set of lineages. Each of the samples was de novo assembled into a single contig. This set of full-length assemblies is a unique collection of genomes from highly drug resistant *M.tuberculosis* strains, which enables detailed investigation of the genomic underpinnings of resistance and virulence in tuberculosis.

**Acknowledgements:** We would like to acknowledge the TB Portals Program consortium members for making the samples available for sequencing and analysis. In addition, we would like to acknowledge the NIH NISC Lab for sequencing and de novo assembly of the genomes.

### EP-TBS-56 Genome-wide detection of epistasis in antibiotic resistant *M. tuberculosis*

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*Mycobacterium tuberculosis* is a globally prevalent bacterial pathogen with increasing resistance to antibiotics. While prior work has identified individual resistance-conferring mutations, the evolution of stable, high-level antibiotic resistance is frequently a multi-step process. A complete understanding of the evolutionary routes to antibiotic resistance would allow us to better understand *M. tuberculosis* biology and forecast new resistance evolution. To date, there have been no systematic studies of epistatic mutations – mutations whose effects depend on their genetic context – in *M. tuberculosis* because the bacterium does not recombine, so variants are rarely observed in multiple genetic backgrounds, meaning that their individual effects cannot be disentangled from their combined effects.

Here, we develop a new phylogeny-based method to determine which mutations are more likely to occur following other mutations in the genetic background. We applied our method to a dataset of over 10,000 *M. tuberculosis* genomes spanning the four major global lineages, and found the top pairs of mutations to be within and between genes involved in antibiotic resistance and host adaptation. We detect compensatory mutations in *rpoC* after the evolution of rifampicin resistance, as well as an apparent multi-step evolutionary process toward high level isoniazid resistance. In addition to finding variants that both compensate for and amplify preceding resistance-conferring mutations, we also find numerous examples of non-independence between the evolution of resistance to different antibiotics, reflecting consistent selection pressures imposed by the standard multi-antibiotic treatment regimens. We expect that this methodology will illuminate the evolutionary routes to antibiotic resistance in *M. tuberculosis*.

### EP-TBS-57 Population structure, biogeography and transmissibility of *Mycobacterium tuberculosis*

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*Mycobacterium tuberculosis* (*Mtb*) is a clonal pathogen proposed to have co-evolved with its human host for millennia, yet our understanding of its genomic diversity and biogeography remains incomplete. Here we use a combination of phylogenetics and dimensionality reduction to reevaluate the population structure of *Mtb*, expanding our understanding of Lineages 2 and 4 and providing the first in depth analysis of the ancient East African Indian Lineage 1 and the modern Central Asian Lineage 3.

We assess sub-lineages using genomic sequences from 4,939 pan-susceptible strains and find 30 new groups that we validate in a dataset of 4,645 independent isolates. We characterize sub-lineage geographic distributions and demonstrate a consistent geographically bounded and unbounded pattern for 20 groups including 3 groups of Lineage 1.

We assess transmissibility of the four major lineages by examining the distribution of terminal branch lengths across the unified *Mtb* phylogeny and identify evidence supporting Lineages 2 and 4 as more transmissible than 3 and 1 on a global scale. We define a robust expanded barcode of 97 single nucleotide substitutions (SNS) that allows for the identification of 71 *Mtb* sub-lineages and 26 additional internal groups.

Our results paint a higher resolution picture of the *Mtb* phylogeny and biogeography. We expect the expanded *Mtb* classification to be useful for applications such as the rapid assessment of potential outbreaks and isolate triage for detailed phylogenetic or phenotypic analyses.

### EP-TBS-58 Safety and efficacy of an MDR-TB all-oral short-course regimen in China: an preliminary analysis of the MDR-Chi clinical trial

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**Background:** Due to lack of safety and efficacy evidence, the uptake of the new all-oral MDR-TB regimens recommended by WHO remained slow in China. Bedaquiline became available in China since 1 Jan 2020, not involved in this study yet.

**Methods:** MDR-Chi is a prospective single-center open-labeled non-randomized controlled trial in China, one arm of which being linezolid/moxifloxacin/cycloserine/clofazimine/pyrazinamide for nine months [ChiC-

TR2000032298]. If pyrazinamide-resistant, prothionamide will be the substitute drug. If fluoroquinolone-resistant, prothionamide will substitute, and the course extended to 12 months. If prothionamide is resistant too, the patient will be dropped out of the trial.

**Results:** 76 patients were enrolled in the linezolid/moxifloxacin/cycloserine/clofazimine/pyrazinamide arm, 14 were fluoroquinolone-resistant (18.4%), 48 (63.2%) had extensive TB disease, 25 (32.9%) had extrapulmonary TB, 6 (7.9%) lost to follow-up.

Of the 76 patients, 69 had taken drugs for over six months until now. 60 (87.0%, 60/69) had a positive baseline culture, and 55 patients (91.7%, 55/60, including the ) experienced culture conversion within two months and 47 (100.0%, 47/47) within six months. Nine (11.8%) patients were cured, 7 with a 9-month treatment, and 2 with 12-month, no relapse in 3 months after cure. Some drugs held responsible for serious AEs were discontinued: linezolid in 3.9% (2.6%, 2/76, due to myelosuppression; 1.3%, 1/76, neuropathy) and moxifloxacin in 1.3% (1/76, QT prolongation) and clofazimine in 1.3% (1/76, QT prolongation) and cycloserine in 1.3% (1/76, psychiatric) of patients.

The peripheral neuropathy (93.4%, 71/76) due to linezolid were manageable and myelosuppression (3.9%, 3/76) was uncommon. Because of skin discoloration of clofazimine, 5.3% (4/76) patients refused to use it, and 2.6% (2/76) discontinued it, and 65.8% (50/76) complained about inconvenience in daily life.

**Conclusions:** MDR-TB patients using the all-oral short-course regimen experienced high culture conversion within two and six months. The toxic effects of drugs were endurable and manageable.

### EP-TBS-59 Drug exposure and minimum inhibitory concentration predict pulmonary tuberculosis treatment response

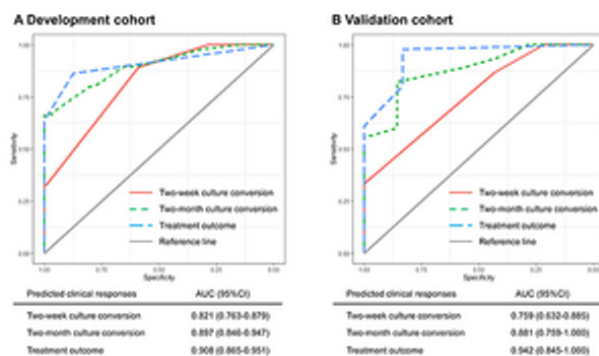
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**Background:** Prospective studies correlating pharmacokinetic/pharmacodynamic (PK/PD) indices to clinical response of tuberculosis are urgently needed. This study aimed to find clinically relevant PK/PD thresholds that can be used for tuberculosis treatment optimization.

**Methods:** Drug concentration and minimum inhibitory concentration (MIC) measurements were performed for patients with culture-confirmed tuberculosis. Classification and regression tree (CART) analysis was applied to obtain PK/PD thresholds for first-line drugs predic-

tive of two-week/month sputum culture conversion and treatment outcome. The association between CART-derived thresholds and time to culture conversion was investigated by Kaplan-Meier survival analysis. Least absolute shrinkage and selection operator (LASSO) logistic regression was used for model development and validation.

**Results:** Finally, 168 and 52 patients with tuberculosis were included in a development and a validation cohort for analysis, respectively. Patients with area under concentration-time curve (AUC)/MIC below CART-derived thresholds for pyrazinamide of 8.52 [odds ratio (OR): 0.15], pyrazinamide of 2.84 (OR: 0.46) or rifampicin of 438.91 (OR: 0.84) had less probability to achieve two-week culture conversion, two-month culture conversion or treatment success, respectively. Patients with PZA AUC/MIC above 8.52 accounted for 9.5% (16/168) and 94.0% of them achieved sputum culture conversion within one month. For those with PZA AUC/MIC below 2.84 (31.5%, 53/168), only 9.0% achieved culture conversion within one month. Apart from PK/PD indices, clinical features, such as extensive pulmonary disease (Timika score  $\geq 71$ ), time to culture positivity ( $\leq 15.5$  days) or diabetes, were also selected by LASSO for prediction of treatment response. The predictive performance of trained LASSO models in validation cohort was evaluated by receiver operating characteristic curves and ranged from 0.759 to 0.942.



[Figure.]

**Conclusions:** PK/PD indices of pyrazinamide and rifampicin were associated with time to sputum culture conversion and treatment outcome, respectively. The effect of individualized dosing using CART-derived thresholds regarding treatment outcome should be studied in a randomized controlled trial.

## EP-TBS-60 A novel therapeutic vaccine against multi-drug resistant tuberculosis by T cell-immunity in phase 1 clinical trial

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Multi-drug resistant (MDR), especially extremely drug resistant (XDR), Mycobacterium tuberculosis (M. TB) is a big problem in the world. We have developed novel TB therapeutic vaccine (HVJ-E/HSP65 DNA +IL-12 DNA vaccine) to eliminate MDR-TB by T cells. DNA vaccine expressing M. TB heat shock protein 65 and IL-12 was delivered by the hemagglutinating virus of Japan (HVJ)-envelope.

**Results:** This vaccine provided remarkable therapeutic efficacy against MDR-TB and XDR-TB in murine models (decrease in the number of MDR-TB). Furthermore, this vaccine provided therapeutic efficacy of prolongation of survival time (100% survival) of TB infected monkeys and augmented the T cell immune responses. Preclinical study by using monkeys in GLP level, safety of the vaccine was shown.

Phase1 Investigator-initiated clinical trial

Therefore, phase 1 clinical trial has been already started. Targets are human patients with MDR-TB. Primary evaluation is safety and tolerability. Secondary evaluation is anti-TB efficacy (sputum-culture conversion). A patient of First Patient In showed safety and tolerability of this therapeutic vaccine by pDNA concentration in the blood.

collecting sputum	before vac.	14 d after vac.	28 d	42 d	98 d	126 d	147 d
gaffky scale	±	±	±	-	-	-	-
colony number	58,333	195	1,000	667	0	0	0
IFN-γ and IL-2	-	increase	increase	-	increase	increase	not done

[Table. Negative conversion of MDR-TB by therapeutic DNA vaccine]

Furthermore, anti-TB efficacy (MDR-TB negative conversion) was demonstrated by the Gaffky study and colony count of TB in the sputum. Anti-TB immunity (IFN- $\gamma$  and IL-2 production) was augmented in the patient with this vaccination from 14~126 day.

**Conclusion:** These data indicate that HSP65 DNA+IL-12DNA vaccine might be useful against XDR-TB and MDR-TB through T cells for human therapeutic clinical applications. (This research was supported by AMED, Japan.)

### EP-TBS-61 Improving the safety of TB therapy with novel diagnostic biomarkers of liver toxicity – a study in UK and Ugandan patients

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Treatment of tuberculosis (TB), including use of novel regimens, can be limited by drug-induced liver injury (DILI). The novel biomarkers microRNA-122 (miR-122) and cytokeratin-18 (K18) have FDA support as diagnostic and prognostic DILI biomarkers in the context of paracetamol-induced liver injury. This study investigates the utility of these biomarkers for diagnosing DILI in the context of TB therapy in the UK and Uganda.

UK patients receiving anti-TB therapy were recruited into the ALISTER study at the Royal Infirmary of Edinburgh. Ugandan HIV-infected patients with active TB, receiving anti-TB and ART therapy were recruited into the SAEFRIF trial at the Infectious Diseases Institute, Kampala. Serial blood samples were collected. K18 was quantified using the M65 ELISA and miR-122 using PCR. Alanine aminotransferase (ALT), the current gold standard DILI marker, was quantified in hospital laboratories.

235 participants were included (healthy volunteers n=28), (ALISTER: active TB n=30, latent TB n=88, non-tuberculous mycobacterial infection n=25), (SAEFRIF: HIV-infected patients with active TB n=64). Across all groups, in individuals with normal ALT ( $\leq 50$  IU/L), there was no significant difference in miR-122 and K18, suggesting that the presence of different mycobacterial infections, or HIV, did not affect assay performance. There was a significant correlation between ALT and miR-122 ( $r=0.52$ ) and ALT and K18 ( $r=0.42$ ). Individuals who developed elevated ALT ( $>50$  IU/L) compared to normal ALT ( $\leq 50$  IU/L) exhibited an 8.0-fold increase in miR-122 (ROC-AUC=0.93) and a 2.3-fold increase in K18 (ROC-AUC=0.80). In the two cases of DILI in this study, miR-122 and K18 both substantially increased.

In conclusion, both miR-122 and K18 correlate with ALT and can report anti-TB DILI. Future clinical trials of anti-TB therapeutics, and studies of anti-TB DILI, should include miR-122 and K18 to further characterise the diagnostic and prognostic performance of these toxicity biomarkers as tools to improve the safety of TB treatment.

### EP-TBS-62 Tuberculosis meningitis mouse model

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**Background:** Tuberculous meningitis (TBM), the most severe form of *Mycobacterium tuberculosis* (*M.tb*) infection involves the central nervous system (CNS), usually afflicts children, and results in a high mortality rate. The *Bacillus Calmette Guerin* (BCG) vaccine protects children below 5 years of age against TBM. Advancement to develop more effective therapeutics and vaccines is hindered by the lack of physiologically appropriate animal models. The current animal models for TBM utilize direct intracerebral or intravenous brain injections thus, bypassing the blood-brain barrier (BBB). In the current study, we assessed the utility of a novel, physiologically appropriate, TBM animal model. *Foxn1Δ/Δ* mouse strain contains mutations in the thymic epithelial cell (TEC)-specific transcription factor, FOXN1. *Foxn1*, affects TEC differentiation, thymus function, and T cell function. This mutation should not affect the permeability of BBB or any other physiological functions.

**Design:** Eight week and five-10 day old *Foxn1Δ/Δ* and *Foxn1+/Δ* mice were infected with *M. tuberculosis* strain Erdman intranasally using a pipette or via the aerosol route in a Madison chamber. The animals were euthanized at humane end point or at study termination, the organs collected and plated for bacterial counts. Lung and brain homogenates were analyzed to detect pro-inflammatory cytokines and matrix metalloproteinases (MMPs) activity.

**Results:** Our data show that both *Foxn1Δ/Δ* newborn and adult mice, compared to the heterozygous *Foxn1+/Δ* mice, infected via the natural route show hematogenous dissemination to extrapulmonary areas including the brain. Lung and brain tissues show increased pro-inflammatory cytokines/chemokines including IL-6, TNF- $\alpha$ , and MCP-1 and functional MMPs in the brain homogenates of *Foxn1Δ/Δ* mice compared to the heterozygous controls.

**Conclusion:** *Foxn1Δ/Δ* mice is a potential model for TBM. Future studies will include larger numbers of infected animals per group to define the mechanism for CNS infection, efficacy assessments of novel anti-tubercular drugs, and BCG protection mechanisms.

### EP-TBS-63 Pharmacokinetics of the three-drug fixed-dose dispersible tablet in children

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**Introduction:** One of the problems in the treatment of children with tuberculosis is the lack of pediatric dosages of anti-TB drugs. It is relevant today to use of child-friendly Fixed Dose Combination (FDC), also supported by the World Health Organization (WHO). FDC has been proven to present therapeutic advantages compared reduce tablets, due to increased compliance and error avoidance.

**Objective:** To assess the clinical pharmacokinetics of a 3-FDC (isoniazid(INH) 150 mg + pyrazinamide(PZA) 375 mg+ rifampicin(RIF) 150 mg) dispersible tablet.

**Methods:** The study enrolled 22 children aged 1–17 years with TB. Patient groups were comparable by gender, age, clinical, radiological and laboratory. In I group (n = 11) 3-FDC dispersible tablets in combination with ethambutol(EMB) and in II group (n = 11) single tablets (ST) of INH, RIF, PZA and EMB were taking into account age-related dosages. Blood samples were collected predose 0 hours and at 2, 4, 24 postdose.

**Results:** Figure 1 – concentrations RIF; figure 2 - concentrations INH.

**Conclusions:** In conclusion, the population pharmacokinetics of first-line anti-TB drugs for children with TB were well described by the final models we established: C<sub>max</sub> for RIF was 15,18±9,05, AUC 79,49±52,93 and T<sub>1/2</sub> 3,75±0,56; C<sub>max</sub> for INH was 2,16±1,41, AUC 10,43±6,15 and T<sub>1/2</sub> 4,17±0,54. Further studies are warranted to determine of C<sub>max</sub> and AUC, especially, for PZA and EMB for the development of optimal dosing in childhood TB.

### EP-TBS-64 Does BCG vaccination protect against infection with Mycobacterium tuberculosis in Vietnamese schoolchildren?

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**Background:** BCG vaccination is known to prevent tuberculosis disease in young children. Whether it protects against infection by Mycobacterium tuberculosis (MTB) remains a subject of controversy and may vary according to geographical latitude. We investigated the association between BCG vaccination at birth and infection by MTB as ascertained by the tuberculosis skin test (TST).

**Methods:** We performed a secondary analysis of data from 3 tuberculin skin test (TST) surveys done amongst Vietnamese schoolchildren between 1988 and 2001. We investigated whether BCG vaccination was associated with a lower prevalence of a positive TST, adjusting for BCG-induced TST variation by applying different cut-off values for a positive TST. Simple and multivariable logistic regression analysis were performed to determine the odds ratio (OR) for a positive skin test (thus infection by MTB) in children with a BCG scar versus children without a BCG scar. This was repeated for increasing cut-off values for a positive TST.

**Results:** At the lowest cut-off value (10mm), the OR for a positive TST in the children with a BCG scar compared to those without was > 1.8 in all regions, and even as high as 3 in the North. The OR decreased as the TST cut-off increased, however it never dropped significantly below 1 even at very high cut-off values, irrespective of region (North, Central or South).

**Conclusions:** We found that BCG vaccination was not associated with reduced MTB infection prevalence using TST. This is contrary to a similar study conducted in Tanzania where children with a BCG scar had a lower risk of TST positivity than those without a scar using the same analysis methods. These opposite findings could be ascribed to geographical differences and the relatively high prevalence in Vietnam of the Beijing genotype that is considered to have the ability to circumvent BCG induced immunity.

### EP-TBS-65 Time to positivity as a surrogate biomarker of time to culture conversion

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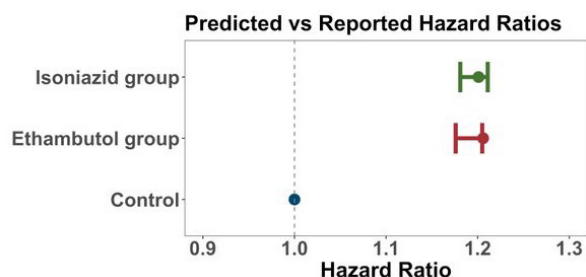
**Background:** Phase-2B clinical trials in TB Drug Development are utilizing time to stable culture conversion (TSCC) as an endpoint. Power analysis is performed based on expected hazard ratio (HR) when comparing intervention to the standard of care arm. Typically, duration of a Phase 2B study is 2-4 months with 60-90 patients per arm.

We hypothesize that using shorter term (up to 6 weeks) longitudinal time to positivity (TTP) data in liquid culture can be equally informative as TSCC in context of decision making. Our goal is to evaluate longitudinal TTP data as a predictor of individual TSCC data and trial level HR.

**Methods:** Patient-level data (n=1733) was pooled from a randomized controlled trial (NCT00864383). Data base included longitudinal TTP, derived TSCC and patient demographic, clinical and treatment factors. A parametric time to event model of TSCC in liquid media was built using a surge function for the hazard and linked to TTP-related predictors.



**Results:** Four predictors were found to be significantly related to TSCC (baseline TTP, slope between baseline and week 6, slope between weeks 2 and 4 and age). Importantly, treatment composition was found not to be influential in defining this relationship. The predicted HR of the trial aligned well with study-reported HR (1.20 vs 1.20 and 1.19 vs 1.21 for isoniazid and ethambutol arm, respectively) (Figure 1), indicating that the HR can be forecasted using shorter-term (6 weeks) data.



[Figure 1.]

**Conclusions:** TTP measured at the beginning of the therapy, and at 2, 4 and 6 weeks can be linked to a model and used as a surrogate biomarker of TSCC, reliably estimating HR. This linkage can be utilized to shorten Phase-2B studies and decrease sample size.

### EP-TBS-66 Use of the contact management register to identify those with Active and Latent TB, Kenya, Jan-March 2020

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**Background:** Contacts of patients with tuberculosis (TB) have an increased risk of developing Latent TB infections (LTBI) and/or TB disease. Contact tracing and screening is a good strategy to timely identify cases of active TB and LTBI thus offering them timely treatment and minimizes on-going transmission.

Kenya has a TB prevalence of 435/100,000; however, it is estimated that 40% of cases are missed. Notification of data from contact management register was introduced in late 2019. TB preventive therapy (TPT) is currently offered to asymptomatic contacts of bacteriological-confirmed cases (BCC) below 5 years of age.

We sought to characterize the contacts of BCC in 5 counties in Kenya, determine the yield of contact investigations for new cases of TB and LTBI and determine the proportion of TB cases which can be prevented by use of TPT through contact investigation.

**Methods:** We conducted a retrospective review of records from contact management register in the national surveillance system, between January-March 2020. A contact was classified as either household, social, work or school.

**Results:** In the 5 counties 1116 contacts of 445 BCC were notified. All were symptomatically screened, there were 64 (6%) presumptive cases of whom 19 (30%) were diagnosed with TB, 18 of these were household contacts. Of the 1116 contacts 196 (18%) were <5 years of age, 190 of them were asymptomatic and 131 were offered TPT. Of the 6 symptomatic children 5 were diagnosed with TB.

**Conclusion:** The register offers a good opportunity to identify, screen and record all contacts of BCC, identify and treat those with TB or those requiring TPT. Scaling up effective use of the register in all counties with major focus on household contacts can help identify the missing cases and those in need of TPT in line with the National TB program goals.

### EP-TBS-67 Predicting efficacy outcome of nine tuberculosis drugs in phase 2a first-in-patients studies

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A clinical early bactericidal activity (EBA) study of tuberculosis (TB) drugs is a short-term study to evaluate the decrease of colony-forming units (CFU) counts of *Mycobacterium tuberculosis* in sputum samples of TB patients over up to 14 days of treatment. Due to its short duration and small sample size, even positive results provide only partial proof-of-concept of efficacy. A translational platform was developed to predict CFU counts in EBA studies using the data from mouse studies.

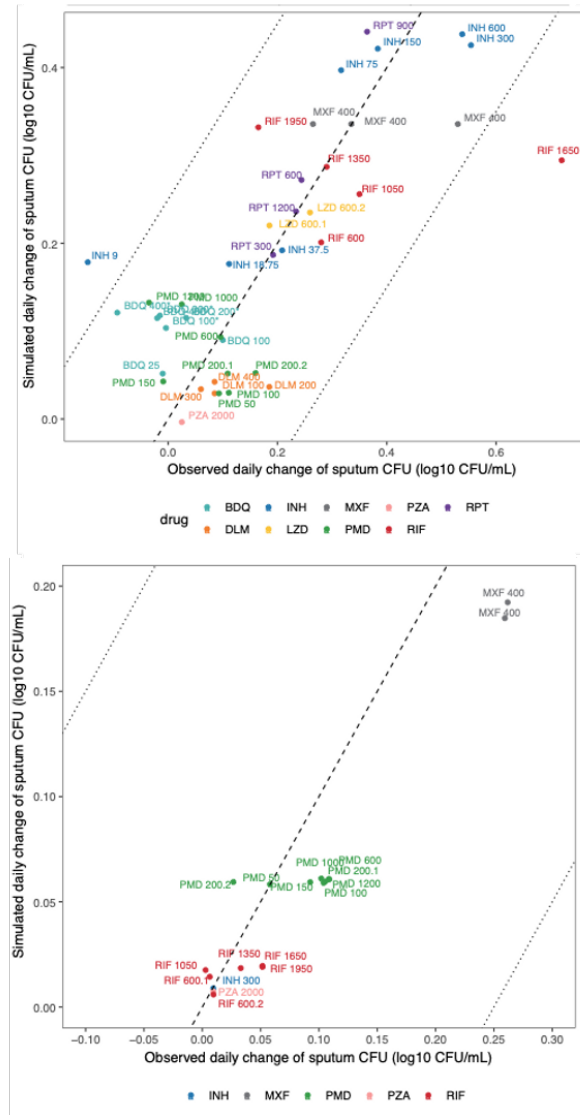
Longitudinal data from 1182 BALB/c mice receiving no drug or dose-ranging therapy were used for model development in NONMEM (v7.4). This translational platform was established upon a baseline model, which describes bacterial replication, death and sigmoidal adaptive immune effect based on bacterial number and incubation time.

Drug effect was incorporated into the baseline model as an additional killing effect. Mouse pharmacokinetics/pharmacodynamics (PK/PD) relationships with a delay effect of rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), bedaquiline (BDQ), delamanid (DLM), linezolid (LZD), moxifloxacin (MOX), pretomanid (PA-824) and rifapentine (RPT) in acute, sub-acute and chronic infection models independent of immune effect were established on the basis of statistical significance and pharmacological meaningfulness.

Goodness-of-fit plots and visual predictive checks were used for model evaluation. Translational prediction of clinical EBA studies was performed using human PK models with the assumption that the PK/PD relationships of these TB drugs are comparable at free plasma concentration levels.



Daily decreases of CFU for each drug during the first 2 days of treatment and between day 2 and day 14 were consistent with clinical observations at multiple dose levels (Fig. 1). This platform may provide an innovative solution to partially replace the phase 2a trial.



[Figure 1: Comparison of predicted and observed changes in CFU counts for nine TB drugs between day 0-2 (top) and between day 2-14 (bottom).]

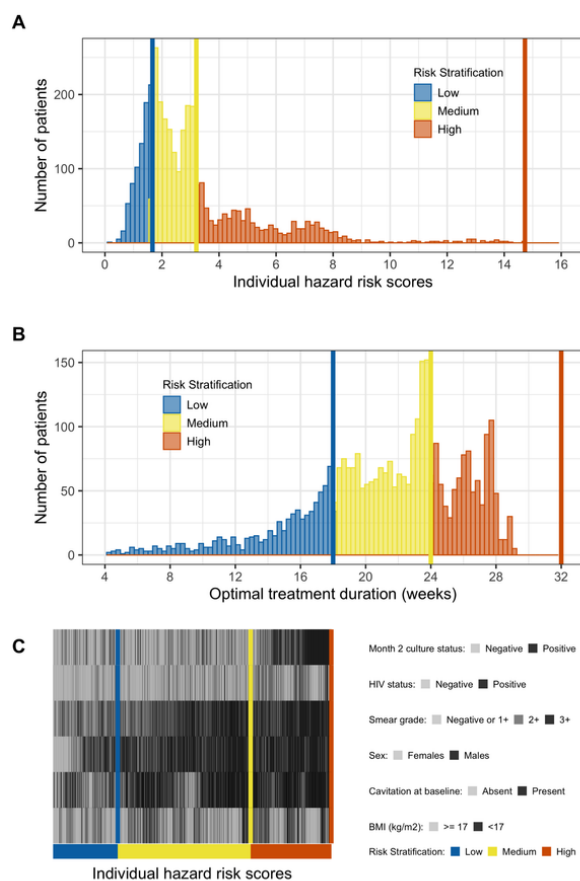
## EP-TBS-69 Predicting optimal treatment durations for tuberculosis patients: a risk stratification algorithm and clinical simulation tool

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**Background:** No evidence-based tools exist to guide decisions on the optimal treatment duration for tuberculosis. We developed (1) survival models to predict individ-

ual risk of unfavorable outcomes, (2) a quantitative risk stratification algorithm that stratifies individuals into risk groups, and (3) a clinical tool that predicts optimal treatment duration of rifampin-containing regimens for each individual.

**Methods:** Data from four Phase 3 trials, each evaluating treatment duration shortening from 6 to 4 months for drug-susceptible tuberculosis were obtained from a public repository. Parametric survival models were used to describe time to unfavorable outcomes. Regimen, baseline, and on-treatment characteristics were evaluated as predictors of outcomes. Exact regression coefficients of significant predictors were used to calculate individual risk scores and a target cure probability of 93% was used to predict optimal treatment durations.



**Distribution of individual risk scores, optimal treatment durations and risk factors.** (A) Distribution of individual risk scores stratified by low, medium and high risk group. (B) Distribution of individual optimal treatment durations for a target cure probability of 93% at 18 months since start of treatment stratified by low, medium and high risk group. (C) Heat map distribution of identified risk factors among low, medium and high risk groups. All individuals are arranged on the x-axis from lowest risk score to highest risk score and each column in each row (risk factor) represents a single individual. Low risk was defined as requiring less than or equal to 18 weeks, medium risk requiring 19 to 24 weeks, and high risk requiring more than 24 weeks of treatment with a standard-dose rifampin-containing regimen for a target cure probability of 93%.

**Results:** A six-item risk score (HIV status, smear grade, sex, cavitation, body mass index and month 2 culture status) successfully grouped participants into low (794/3405, 23%), medium (1624/3405, 48%), and high (987/3405, 29%) risk, requiring treatment durations of 4,

6 and greater than 6 months, respectively, to reach a target cure probability of 93% when receiving standard-dose (10 mg/kg) rifampin-containing regimens. With current one-duration-fits-all approaches, high risk groups have 2.4-fold (95% confidence interval: 1.9-2.9) and 3.7-fold (2.7-5.1) higher risk of unfavorable outcome compared to medium and low risk groups, respectively.

**Conclusions:** Our results show that stratified medicine approaches, where duration is selected with precision based on patient risk, is feasible and safely achieves high cure rates in tuberculosis patients. A validated, interactive, evidence-based tool for selection of optimal treatment durations is provided.

### EP-TBS-70 Adverse drug reactions in MDR TB patients on category IV regimen in Western Odisha

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**Introduction:** MDR-TB imposes a formidable burden on national health care system and poses great threat to destabilize the best efforts of TB control. Use of second line drugs has hiked the economic burden and increased ADR rate. ADR—a major hindrance arises out of non compliance. Early detection and appropriate management of ADRs is the need of the hour.

**Methodology:** All diagnosed MDR- TB patient attended DR-TB centre VIMSAR, Burla from November 2013 to October 2015 were evaluated. Baseline epidemiological, clinical and laboratory data documented on Microsoft excel sheet. Monitoring and documentation of the ADRs was done by direct interview, from treatment card and then managed accordingly.

**Results:** 76(66%) patients suffered from drug related side effects out of which 62 were from low BMI group showing significant correlation between two. GI intolerance (40%) was most common encountered ADR prevalent in early part of treatment. Otolotoxicity(9.56%) was most common severe ADR encountered. 78.9% of ADR managed symptomatically, treatment modification required in 10.5% patients. 2 out of 11 defaulter discontinued treatment due to ADR.

**Conclusion:** More than half of the patient suffered drug related side effect but severe adverse drug reactions observed in very few patients. Risk of ADR more in low BMI patients. Health care providers, patients should be sensitised regarding ADRs. Early detected is half conquered and timely management is full conquered. So individualized treatment regimen should be implemented.

**Keyword:** MDR TB, Adverse drug reaction, Category IV Regimen, Low BMI

### EP-TBS-71 The effect of antiretroviral therapy and preventive tuberculosis therapy with anti-TB drugs on the duration of TB remission in HIV-infected patients

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**Introduction:** According to current national practice, all HIV(+) patient with cured TB are prescribed antiretroviral therapy (ART) and preventive TB therapy (PT) for prophylaxis TB relapse. The effect of both types of therapy on the duration of TB remission was studied in the patients with TB relapse of the main (104 HIV(+) patient) and control (101 HIV(-) patient) groups. The obtained data were checked on 68 cured TB/HIV patients of test group.

**Results:** The duration of TB remission in HIV(-) patients was longer in comparison with HIV(+) patients ( $55.1 \pm 21.8$  months and  $35.1 \pm 12.4$  months respectively,  $p < 0.001$ ). Patients of the main group who received at least 1 course of PT ( $n = 52$ ) or did not receive PT ( $n = 52$ ) had an equally shorter TB remission compared with HIV(-) patients ( $32.1 \pm 17.8$  months,  $31.5 \pm 23.3$  months and  $55.1 \pm 21.8$  months,  $p = 0.009$ ,  $p = 0.008$ ). HIV(+) patients, who did not receive ART or it was ineffective ( $n = 67$ ) had also shorter TB remission compared with HIV(-) patients.

At the same time, in patients with effective ART ( $n = 37$ ), the duration of remission did not differ from that of HIV(-) people ( $27.9 \pm 11.4$  months,  $37.8 \pm 14.6$  months and  $55.1 \pm 21.8$  months,  $p < 0.05$ ,  $p > 0.05$ ). The obtained data were checked in the test group and showed the similar results.

**Conclusions:** Effective ART affects at the duration of TB remission and should be used for prevention of TB relapse. At the same time PT did not affect at the timing of TB remission.

### EP-TBS-72 A urine colorimetric assay for levofloxacin concentrations and optimized regimen development

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**Background:** Levofloxacin is a preferred drug for multidrug-resistant (MDR)-TB and anti-bacterial activity correlates with pharmacokinetic exposures like serum peak concentration ( $C_{max}$ ) and total area under the concentration curve ( $AUC_{0-24}$ ). Pharmacokinetic exposures can be measured to personalize dosing to reach targets, but this practice requires venipuncture, sophis-

ticated chromatographic or mass spectrometry equipment, and technical expertise. We sought to demonstrate the feasibility of using urine colorimetry for estimation of levofloxacin exposure for optimum regimen development.

**Methods:** A colorimetric method using bromocresol green was tested on spiked urine samples and levofloxacin was measured at 440 nm by spectrophotometer. This method was tested in urine samples from six volunteers given one 750 mg dose of levofloxacin with urine was collected at 0-4hr, 4-8hr, and 8-24hr intervals; and concomitant serum samples were analyzed by high-performance liquid chromatography. Further validation was performed in cohort of ten people living with HIV (PLWH) in Irkutsk, Russia, and initiating a levofloxacin containing MDR-TB regimen.

**Results:** Urine colorimetry was reproducible in spiked samples with correlation coefficient values averaging 0.98. In healthy volunteers,  $C_{max}$  ranged from 6.8 to 9.9  $\mu\text{g/ml}$  (target  $>8 \mu\text{g/ml}$ ) and  $AUC_{0-24}$  ranged from 56 to 117  $\text{mg hr/L}$ . Correlation between urine absorbance values and  $AUC_{0-24}$  was highest in urine collected between 4-8hr ( $r=0.96$ ). Receiver operating characteristic curve was 100% sensitive in detecting  $C_{max} >8 \mu\text{g/ml}$  (lower limit of expected range and target for dose adjustment). Similarly, in PLWH, levofloxacin concentration in urine at time 4-8hr had the strongest correlation with both  $C_{max}$  and  $AUC$ ; and absorbance at time 4-8hr correctly classified all 4 participants with above target  $C_{max}$ .

**Conclusion:** Urine levofloxacin absorbance at time 4-8 hr predicted target serum  $C_{max}$ , and showed good discrimination for  $AUC_{0-24}$ . Further field studies are ongoing among people with MDR-TB, which may yield a personalized dosing option in TB endemic settings.

### EP-TBS-73 Development and application of an integrated biomarker - clinical endpoint tool for late stage TB regimen development and clinical trial design

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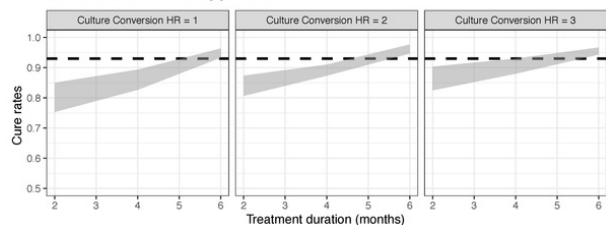
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**Background:** TB regimen development is plagued with many challenges, the most serious being the inability to identify optimal regimens early and efficiently. We developed integrated models that described the translational link between sputum-based Phase 2B intermediate biomarkers, patient risk factors, and treatment characteristics to Phase 3 clinical endpoints at an individual level. We applied our tool to recommend minimum culture conversion targets required for treatment duration shortening. Additionally, we used our tool to design innovative trials that maximize success of late stage TB regimen development with the most promising regimens.

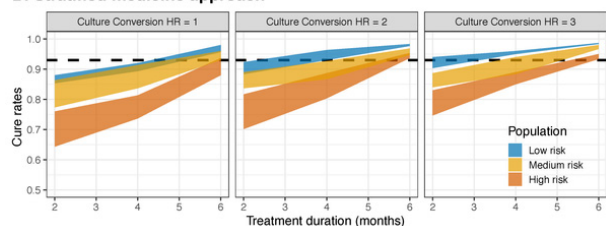
**Methods:** Data from four Phase 3 trials ( $n=4003$ ) that compared six novel regimens to the standard of care treatment for drug susceptible TB was used to develop integrated parametric models. Simulations were performed to assess cure rates of novel regimens with culture conversion hazard ratios (HR) of 2 and 3 for treatment durations between 2 and 6 months. Trial designs with a one-duration-fits-all approach, stratified medicine approaches or adjuvant therapeutic strategies, such as host-directed therapies and therapeutic vaccines, were evaluated to maximize trial success.

**Results:** Potent regimens with culture conversion hazard ratios of 3 or more are required to shorten treatment durations to 4 months using a one-duration-fits-all approach. With these potent regimens, a stratified medicine approach may allow for low risk populations to be treated with ultrashort 2-month durations. Adjuvant therapies have the potential to reduce relapse by 50% if culture conversion hazard ratios are above 1.5 for the same intended duration. Phase 3 designs with innovative stratified medicine approaches or adjuvant therapeutic strategies have potential to introduce superiority tests in the TB regimen development process.

#### A. One-duration-fits-all approach



#### B. Stratified medicine approach



[Figure. Predicted cure rates for novel regimens with Phase 2B culture conversion hazard ratios of 1 (left), 2 (middle), and 3 (right) administered for 2 to 6 month durations. (A) Simulations for one-duration-fits-all approach. (B) Simulations by risk group for a stratified medicine approach. Shaded areas represent uncertainty in relapse after adjusting for culture conversion improvements]

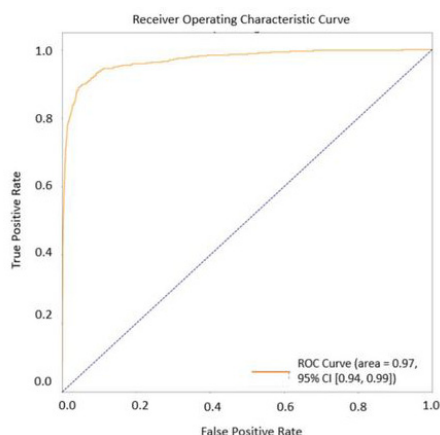
**Conclusions:** We provide a clinical trial simulation tool that can be used to design optimal trials that permit informed decisions about moving the best regimens forward in the TB regimen development process.

## EP-TBS-74 Leveraging neural networks and imaging experts in loops for automated tuberculosis screening using chest radiographs in population screening programs to ensure efficient workflows

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**Purpose:** We developed a deep learning (DL) model to automatically screen chest X-rays (CXRs) for presence of tuberculosis (TB) and customized it specifically for a population screening program with “AI and Expert in Loop Model” to provide a “final signed report”. Deployed at live TB screening site in India, used to process 18,170 CXRs over 3 months. We report model performance, observations, discuss challenges of developing DL models for low prevalence settings like population screening as compared to a hospital-setting where pathology prevalence are typically higher.

**Method and materials:** Active TB screening program run by government body in collaboration with public health foundation, we reviewed CXR dataset of 44,623 images taken in mobile diagnostic vans during the period April to September 2019. Anonymized HIPAA compliant annotated images by a qualified radiologist, who marked each image as either TB-positive or TB-negative. An image that contained following was marked as TB-positive: nodular shadows, infiltrates, pleural effusion, pneumonia or consolidation-like features, fibrosis, pleural thickening, granuloma, bronchiectasis, scarring, lymph node, and calcified pleural plaques. We trained our DL model with 7,039,554 parameters on these images. During live testing, the model generated predictions for 18,170 CXRs taken from October 2019 to December 2019.



[Figure. ROC curve at different classification thresholds]

Accuracy	0.94, 95% CI [0.93, 0.96]
Sensitivity	0.90, 95% CI [0.81, 0.98]
Specificity	0.95, 95% CI [0.93, 0.96]
AUROC	0.97, 95% CI [0.94, 0.99]

[Table. Performance measures for the model]

**Results:** All images were evaluated by an expert radiologist. Model predictions compared to the radiologist readings, model demonstrated an AUROC of 0.97, 95% CI [0.94,0.99], and a sensitivity of 0.90, 95% CI [0.81,0.98], at a specificity of 0.95, 95% CI [0.93,0.96]

**Relevance:** Recognizing early diagnosis is the key to eradicating tuberculosis, governments around the world have started active case-finding through population screening programs. Deploying AI based workflows, DL and experts working collectively provides instant validation and quantified, structured radiology reports. Pre-screening using DL and final reports with experts in loop provides an affordable, scalable last mile approach for population screening solution.

## EP-TBS-75 A model for the integration of traditional medicine into conventional medicine for the treatment of Tuberculosis (TB) in Zimbabwe

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The emergence of new health threats and recurrence of infectious diseases such as Tuberculosis (TB) and HIV/AIDS, have made it impossible for biomedicine to single handedly tackle the ever growing complexities of healthcare provision in modern times. This has led to a global propensity to improve access to traditional medicine (TM) and complementary/alternative medicine (CAM). However, these healing systems are differentiated from conventional medicine (CM) (also called allopathic medicine), and are often excluded from primary healthcare systems of many nations. Like most countries in sub-saharan Africa, the majority of the Zimbabwean population explore TM either as a substitute, or a complement, to CM in the alleviation of diseases including TB and HIV/AIDS. An ethnobotanical survey of TM practitioners (TMPs) in Harare urban was conducted. Exclusive herbalists (5), spiritualists (2) and those who used a combination of spiritualism and herbalism (7) in their practice were recruited for the study. Data was collected through semi-structured in-person interviews. The practices and treatment modalities in the traditional treatment of TB were documented; and some similarities and/or linkages with the conventional system were identified. Primary data on the national TB program, and other relevant information were collected by means of structured in person or telephone interviews of key personnel in the relevant departments at the Ministry of Health and Child Care (MoHCC), the Medicines Control Authority of Zimbabwe (MCAZ) and ZINATHA. Following critical appraisal of primary and secondary data collected, a comparison of TM versus CM was drawn, and a comprehensive model for the effective integration of traditional medicine into the mainstream healthcare system was proposed, in line with recom-

recommendations from the WHO Traditional Medicine Strategy (2014-2023). Such a synergy could offer a more patient centric approach to TB treatment, accelerate UHC, improve comprehensiveness of the health system, and potentially decrease TB burden in Zimbabwe.

### EP-TBS-76 Point-of-care saliva assay for levofloxacin concentrations and personalized dosing in patients with multidrug-resistant tuberculosis in Tanzania

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**Introduction:** A novel point-of-care method using saliva as an alternative matrix for therapeutic drug monitoring (TDM) was compared to standard serum TDM to detect subtherapeutic dosing of levofloxacin (LFX) in Tanzanian multidrug-resistant tuberculosis (MDR-TB) patients.

**Methods:** 51 adult patients recruited at Kibong'oto Infectious Diseases Hospital in July 2019 were on LFX (750 or 1000 mg once daily) for minimum 2 weeks pre-enrollment. Previously validated limited sampling strategies utilized collection times of 1 and 4 hours after dose administration for measurement of LFX serum peak exposure (C<sub>max</sub>) and area under the time concentration curve 0-24 hr (AUC<sub>0-24</sub>). Saliva was collected in the field with concentrations quantified via nanophotometer. Serum was collected and transported to a regional reference laboratory for high-performance liquid chromatography analysis. Receiver operator curve (ROC) s were constructed to compare saliva parameters with conventional serum parameters.

**Results:** 45 patients with 13 (28.9%) women and median age, 20 (39.2% ) with HIV on antiretroviral therapy. Saliva median LFX C<sub>max</sub> was 14.38 µg/ml and AUC<sub>0-24</sub> was µg\*h/ml, while serum median LFX C<sub>max</sub> was 10.86 µg/ml and AUC<sub>0-24</sub> was 134.12 µg\*h/ml. Comparing the key subtherapeutic cut-offs for LFX of C<sub>max</sub> <8 µg/ml and AUC<sub>0-24</sub> <80 µg\*h/ml as determined by serum concentrations, ROC analysis of area under the curve was excellent at 0.89 (95% CI 0.79 - 0.97) and 0.83 (95% CI 0.68 - 0.95) for C<sub>max</sub> and AUC<sub>0-24</sub>, respectively, and saliva was 100% sensitive and 82% specific in identifying patients with both subtherapeutic C<sub>max</sub> and AUC<sub>0-24</sub> that would require levofloxacin dose increase.

**Conclusions:** In this proof-of-concept study, a nanophotometer was able to quantify saliva LFX concentration to determine subtherapeutic drug exposure patients treated for MDR-TB, particularly in settings without access to chromatography or mass spectrometry.

### EP-TBS-77 PBPK model informed prediction to evaluate the effect of renal impairment and OCT genotypes on the ethambutol disposition

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**Background:** Ethambutol is a first line antituberculosis drug and renal elimination is the major route of elimination. Previously, ethambutol has been characterized as a substrate of organic cation transporters. Among terminally renal failure patients has been observed a significant higher ethambutol plasma level than normal renal function. As a result, it is worthy enough to evaluate renal function and transporter PGx, drug-interactions and interplay among them on ethambutol pharmacokinetics. Therefore, we aimed to develop PBPK model implying those variables to understand more in detail.

**Methods:** Using in vitro stably transfected cells with OCT2 wild and mutant type OCT2-T199I, we estimated transport kinetics for ethambutol and inhibition kinetics (K<sub>i</sub>) with cimetidine (OCT2 inhibitor). Later on, we developed a whole-body, mechanistic kidney PBPK model (1200 mg ethambutol, 400mg cimetidine) using Simcyp (V 17) among differential GFR group (healthy, 30-60, 15-30) to see renal impairment effect.

**Results:** OCT2-genetic variants showed significant ethambutol transport difference in vitro compared to wild type. The ethambutol and cimetidine with OCT2-T199I variant PBPK model predicted an increased AUC 1.25 fold higher than wild type group, and no significant PK alteration by cimetidine among wt and mt group. Furthermore, an increased AUC ratio 1.35 and 1.50 among GFR 30-60 and 15-30 groups, with significant reduced renal clearance than healthy. Most importantly, terminally impaired GFR and OCT2-T199I combined caused ~2 fold increase of ethambutol AUC, reduced ~3 fold renal clearance than healthy subjects.

**Conclusion:** This is the first PBPK model showed significant effect of renal impairment and transporter-PGx on ethambutol PK, roadmap towards personalized dose estimation.

### EP-TBS-78 Development of population pharmacokinetic model of the first-line anti-TB drugs in Korean patients with TB for therapeutic drug monitoring guided dose adjustment

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**Background:** Therapeutic drug monitoring (TDM) guided individualized anti-tuberculosis (TB) therapy of the first-line anti-TB drug regimen reduces the risk of TB relapse and development of drug resistance. In this study, we aimed to develop the relevant prior pharmacokinetics model for applying to TDM of the first-line anti-TB drugs in Korean TB patients.

**Methods:** An observational cohort study is currently being performed in anti-TB drugs-treated TB patients at the Center for Personalized Precision Medicine of Tuberculosis (cPMTb). For each first-line anti-TB drug, about 100 consecutive patients were collected and randomly distributed into the training group (80% of total patients) and the test group (20% of total patients). Data were analyzed using population pharmacokinetic (PPK) modeling. The predictability of the model for each the first-line anti-TB drug and the corresponding published PPK models previously used in TDM of our center was studied using the test group.

**Results:** The kinetics of all drugs was well characterized using first-order elimination and first-order absorption, with INH described by two-compartment disposition models, and RIF, PZA, and EMB by a one-compartment model. The effect of body size was described using allometric scaling for all drugs except for INH. N-acetyl transferase2 (NAT2) phenotype was identified as a significant covariate affecting INH clearance. Our model predicted the observed concentrations with the more accurate and precise than the corresponding published model for INH, RIF, and EMB whereas it showed similar accuracy and precision to the published model for PZA.

**Conclusion:** The first-line anti-TB drug PPK model developed from routine care of Korean TB patients show reasonable predictive performance in a small external validation dataset.

### EP-TBS-79 Model informed personalized dosing algorithm development for TB therapy in center for personalized precision medicine (cPMTb)

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**Background:** Ultimate goal of model-informed precision dosing (MIPD) using Population PK and physiology based PK (PBPK) model is maximizing efficacy and minimizing toxicity by patient drug response based individualizing regimens.

Unfavorable outcome TB patients are predominantly driven by high inter-individual variability of anti-TB drug response. MIPD applied TB treatment, especially for MDR TB or XDR TB, is expected to reduce the incidence of preventable ADR (adverse drug reactions) and improvement of the efficacy.

**Mission:** Personalized precision dosing algorithm development for anti-TB drug treatment and its practical application to end TB epidemic.

**Strategies & current progress:** Firstly, our center is constructing multi-site clinical TB cohort including over than 5000 Korean or Southeast Asian TB patients. The cohort database collects patient's clinical information such as TB diagnosis, TB treatment regimen, demographic, laboratory data, comorbidity and co-medication, anti-TB drug concentrations for therapeutic drug monitoring (TDM), MIC, genetic and metabolomic biomarker, ADR etc. We are supporting TDM guided dose adjustment for clinical sites using prior Population PK model and Bayesian method and developing and updating our Population PK model based on the cohort database. Although the current data is not sufficient, we are reconfirming the usefulness of TDM guided individualized dose adjustment in TB therapy from our database.

We also investigate the potential genetic, metabolomic, or transcriptomic biomarkers for ADR using omics technologies. Secondly, we are constructing a comprehensive database for all anti-TB drugs from intensive literature review and in-house experiments, which contains physico-chemical characteristics, in vitro ADME, clinical PK or PD data, etc. Based on this database, we are developing specific PBPK models for diverse clinical settings which cannot be covered by Population PK model. From the developed Population PK and PBPK model, we will construct the personalized precision dosing algorithm for initial dose prediction or dose adjustment in TB pharmacotherapy.



## EP-TBS-80 Classifying adherence trajectories: an innovative tool for regimen development

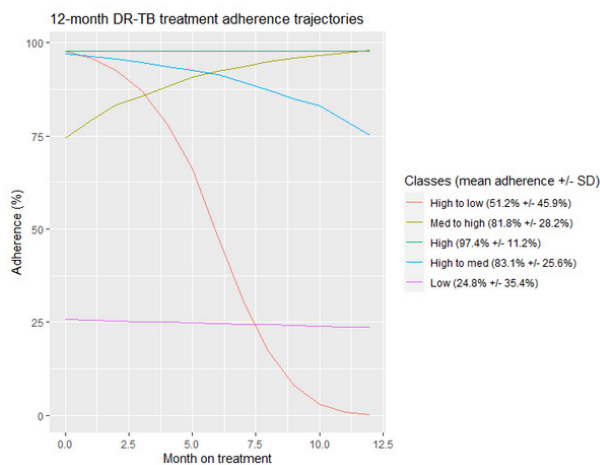
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**Background:** Treatment adherence has been shown to influence the relative effectiveness of TB treatment regimens (Imperial et al., *Nature Medicine*, 2018). Regimen characteristics can affect adherence and are important for novel regimen development. However, there is limited research on informative patterns of treatment adherence, particularly in longer drug-resistant (DR) TB treatment.

**Methods:** We classified 12-month treatment adherence trajectories for 2053 DR-TB patients enrolled in the endTB observational study, a 17-country study of DR-TB treatment containing bedaquiline and/or delamanid. We compared latent class growth mixture models and selected the best model according to statistical criteria. We estimated the association between trajectory classes and treatment outcomes using multinomial log-linear models, adjusted for potential baseline confounders.

**Results:** The final model identified 5 distinct adherence patterns: high (n=1570, 76.5%); high to medium (n=136, 6.6%); medium to high (n=162, 7.9%); high to low (n=77, 3.8%); and low (n=108, 5.3%).



[Figure.]

Compared to the “high” adherence group, those in “medium to high” or “high to medium” had similar risks of death or treatment failure; the “medium to high” group had significantly lower odds of loss to follow-up (odds ratio (OR) 0.00006 (95%CI 0.0000061, 0.0000068)) while the latter group had increased odds (OR 18.7 (95%CI 7.2, 48.6)).

Simple mean adherence ranged from 81.8% to 97.4% among these three groups. Those classified as having “high to low” or “low” adherence trajectories had lower mean adherence and significantly higher odds of death, treatment failure, or loss to follow-up.

**Conclusion:** Latent class growth mixture models represent an innovative tool to classify adherence to longer DR-TB treatments. They provide more insight into patient adherence dynamics than traditional static approaches of classification. The differential effects of adherence trajectory classes motivate the value of evaluating adherence trajectories in regimen development. Regimens that have more consistent effects across adherence trajectories would be more robust.

## EP-TBS-81 Predicting pretomanid penetration into patient lesions of tuberculosis

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Pulmonary tuberculosis (TB) presents with hallmark heterogeneous lesions that harbor the causative bacterial pathogen. To effectively sterilize and reduce risk of relapse, anti-TB drugs must access these sites at therapeutically relevant concentrations. Currently, the extent of lesion penetration in patients for the recently approved drug, pretomanid (PTM) is unknown.

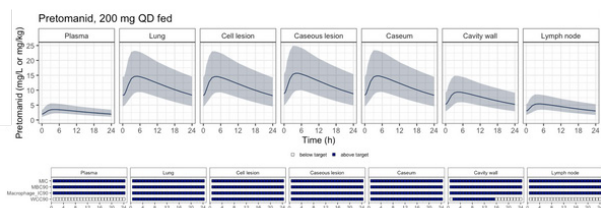
In this study, the pharmacokinetics (PK) of PTM from plasma to 6 distinct lesion types in rabbits was modeled, and through integration of a clinical plasma PK model, the lesion exposure in patients was simulated.

Rabbits were orally dosed with 5-50 mg/kg of PTM and a human-equivalent dose of 20 mg/kg was selected for lesion PK studies where rabbits were dosed daily for up to 13 days. PTM was quantified in serial plasma samples and in 6 distinct lesion types (515 total lesion samples) by liquid chromatography tandem-mass and laser capture microdissection. The data were modeled with NONMEM software using standard practices.

PTM rabbit plasma PK were well-described by a one-compartment model with first-order absorption and elimination. For all lesions, > 4-fold PK accumulation was observed compared to plasma, indicating good penetration properties. Upon integration with a clinical plasma PK model, the expected human lesion PK were simulated and quantified against various in vitro targets.

Following administration of recommended daily 200 mg dose with food, PTM time above minimum inhibitory and bactericidal concentration and macrophage IC90 at steady state were maximal (100%). Time above Wayne cidal concentration (7.19 mg/L) were maximal for 4 of 6 lesions, partial for cavity wall (14/24 hours), and zero for plasma and lymph node.

The favorable accumulation of PTM in lung tissue and infected lesions supports use of PTM as a partner drug in regimens for the treatment of pulmonary TB. Understanding lesion penetration can guide dose optimization and aid in drug prioritization and regimen construction.



[Figure.]

### EP-TBS-82 Rifapentine pharmacokinetics and pharmacodynamics: murine and human models to identify optimal dosing for treatment of latent *M. tuberculosis* infection

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**Background:** Rifapentine has facilitated the shortening of latent tuberculosis infection (LTBI) treatment in combination with isoniazid to 3 months with once weekly dosing (3HP) and 1 month with daily dosing (1HP). Given the efficacy and potency, novel rifapentine monotherapies are now being explored, which could improve safety by eliminating isoniazid use. We performed clinical and translational pharmacological modeling to identify appropriate dosing of a rifapentine monotherapy regimen and predict clinical efficacy.

**Methods:** Rifapentine and isoniazid pharmacokinetics were simulated using population pharmacokinetic models in mice and humans to predict drug exposures and pharmacokinetic-pharmacodynamic (PK-PD) indices with short-course LTBI regimens: 3HP, 1HP, and 6 weeks daily rifapentine (6wP). CFU data from mouse efficacy studies were used to characterize the exposure-response relationships of 1HP, 3HP, and 6wP and translated to humans to predict clinical efficacy.

**Results:** Clinical dosing simulations showed that 600 mg (vs. 300 mg) of 6wP delivered more cumulative rifapentine exposure than 1HP or 3HP. Rifapentine pharmacokinetics and PK-PD indices at equivalent doses were similar in mice and humans. The PD model predicted mouse CFU data well. Estimated rifapentine potency (EC<sub>50</sub>) in LTBI was 13.2 mg/L when given alone. In combination with isoniazid, rifapentine potency was increased: adjusted rifapentine EC<sub>50</sub> = 3.27 mg/L for 3HP and adjusted EC<sub>50</sub> = 11.9 mg/L for 1HP. This suggests

that isoniazid contributes little to efficacy when given with daily rifapentine. Translating to humans, 6wP was predicted to reduce tuberculosis burden faster than 3HP and to a greater extent than 1HP.

**Conclusions:** Rifapentine 600 mg daily for 6 weeks is predicted to result in equal or better efficacy than 1HP and similar efficacy to 3HP for LTBI treatment without added exposure to isoniazid that may result in unnecessary toxicity. Results from ongoing and future clinical studies will be required to support these findings.

### EP-TBS-83 *SLCO1B1* and *SLC10A1* polymorphism and plasma rifampin concentrations in patients with co-morbidity tuberculosis-diabetes mellitus in Baja California, Mexico

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Worldwide, there has been an increase in type 2 diabetes mellitus (T2DM) as a comorbidity of tuberculosis (TB), which is characterized by alterations in the pharmacokinetics of TB drugs. Rifampin plasma concentrations in TB patients might vary by T2DM and HIV infection among other factors. Polymorphisms in *SLCO1B1* and *SLC10A1* genes are associated with impaired transporter function of drug compounds such as rifampin.

The relationship between genetic variation and rifampin exposures in TB patients has not been completely elucidated. The objective of this work was to determine the effect of *SLCO1B1* and *SLC10A1* gene polymorphisms on rifampin concentrations in TB and TB-T2DM patients from México.

Blood samples were collected in two hospitals in Baja California, Mexico from March through December 2017. Sampling included 14 patients with TB, 16 with T2DM, and 17 healthy individuals. Genotyping of polymorphisms rs2306283, rs4149056, rs11045819, and rs2291075 of *SLCO1B1* and rs464628 and rs138880008 of *SLC10A1* was performed by Sanger's sequencing. Chi-squared tests for Multiway Contingency Tables were used for the analysis of the frequencies of the polymorphisms.

The *SLCO1B1* rs2306283 and rs4149056 polymorphism were present in both TB and T2DM individuals, like heterozygous for the variant allele. Although, rs11045819 and rs229107 were homozygous for the wild allele in both TB and T2DM patients. The *SLC10A1* rs4646285 and rs138880008 polymorphism were present in all individuals. None of the *SLCO1B1* and *SLC10A1* genotypes were significantly associated with rifampin C<sub>max</sub>.

TB and T2DM patients with suboptimal Cmax rifampin levels showed wild alleles in rs11045819 and rs2291075 in *SLCO1B1*. This is the first study to analyze *SLCO1B1* polymorphisms in TB and T2DM patients in Mexico. Further research to confirm and extend these findings is necessary.

### EP-TBS-84 Individual-level data meta-analysis of adverse events from clinical trials of drug sensitive tuberculosis treatment regimens

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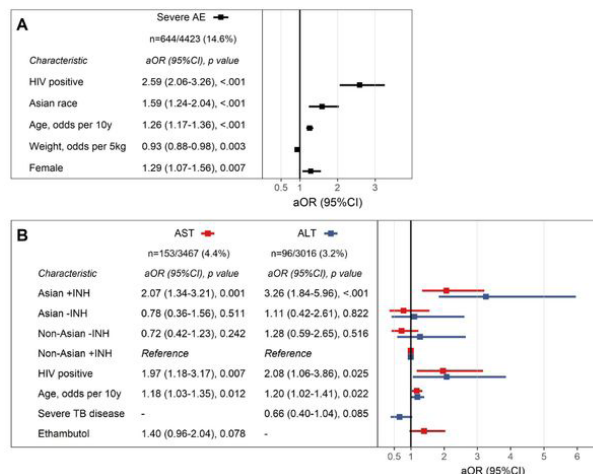
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**Rationale:** Knowledge of the safety and toxicity of tuberculosis (TB) regimens is essential for optimizing adherence, treatment completion and clinical trial design. **Objectives:** Characterize adverse events (AE) associated with the current standard regimen for drug-sensitive TB using a large dataset from contemporary randomized controlled trials.

**Methods:** Patient individual-level data from OFLOTUB, REMoxTB, and RIFAQUIN trials (n=4447) were pooled. AEs were mapped over time in standard of care and experimental fluoroquinolone-containing regimens. Multivariate logistic regression was performed to determine best predictors of severe AEs and liver enzyme shifts (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), defined as elevations from baseline to >3-10 times the upper limit of normal.

**Results:** Severe AEs occurred in 14.6% [n=649/4447] of patients and liver enzyme shifts in 5.1% of patients tested (AST: 4.4% [n=153/3467]; ALT: 3.2% [n=96/3016]). Half of the safety episodes documented occurred during the 2-month intensive phase of therapy (severe AE: 48.9% [n=486/994]; AST shift: 47.5% [n=106/223]; ALT shift: 63.6% [n=96/151]), 25.8% were recorded in the continuation phase and 23.9% during post-treatment follow-up. After adjusting for other factors, we found that HIV positive patients regardless of TB-treatment regimen were 2.59 times more likely to have severe AE (aOR=2.59[2.06-3.26]) and twice as likely to have AST (aOR=1.97[1.18-3.17]) or ALT (aOR=2.08[1.06-3.86]) shift. Patients of Asian race were 59% (aOR=1.59[1.24-2.04]) more likely to have severe AE regardless of regimen, but Asians treated with isoniazid were twice as likely to have AST shift (aOR=2.07[1.34-3.21]), and 3 times more likely to have ALT shift (aOR=3.26[1.84-5.96]) compared to others on isoniazid-containing regimens. Presence of fluoroquinolone in the regimen did not impact the safety profile.

**Conclusions:** Analysis of data from contemporary TB clinical trials showed that the standard of care regimen should not be considered universally safe. We have identified patient phenotypes at risk of severe AE. This analysis represents the current safety benchmark for future studies.



[Figure. Characteristics associated with having a safety event, multivariate models adjusted for clinical trial (REMOxTB, OFLOTUB, and RIFAQUIN).

(A) Predictors of severe AE, (B) Predictors of AST and ALT liver enzyme shifts.]

### EP-TBS-85 G-clamp-inspired ligands and their effects on G-quadruplexes from Mycobacterium tuberculosis

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G4-stabilizing ligands are now being considered as anticancer, antiviral, and antibacterial agents. Despite recent advances in the development and application of such agents, the search for new ligands, especially those that selectively recognize G-quadruplexes (G4s) in the presence of an excess of dsDNA, is ongoing.

The aim of the present study was to synthesize new phenoxazine-based ligands and to evaluate their effects on genetically stable G-quadruplexes from Mycobacterium tuberculosis.

Genomic analysis of approximately 750 genomes, representing seven phylogenetic lineages, revealed 122 high-scoring and genetically stable putative G4s motifs in genes, essential for mycobacterial growth and virulence. Additionally, 59 genes with putative G4s, upstream or overlapping their TSS, were found. Eight mycobacterial G4s were synthesized for analyzing their interactions with two new phenoxazine-based ligands in FRET-melting experiments. G4-stabilizing properties and duplex versus G4 selectivity were assessed and compared with the existing G4-interacting small molecules NMM, PDS, and BRACO-19. Therapeutically significant G4 targets from the human genome (telomeres and the cKit

oncogene promoter) were used as a control. The new ligands with protonated amino-/guanidino-containing tethers exhibited profound effects on genetically stable G4s from *M. tuberculosis*, as well as on human telomeric and oncopromoter G4s. Among them, the ligand with amino-containing arms was a particularly efficient G4 stabilizer, superior to NMM and PDS, and unlike BRACO-19, it showed high selectivity for G4s over duplexes.

In view of the selectivity and the remarkably high stabilizing effects on *M. tuberculosis* and human G4 targets, this ligand may have therapeutic potential as an antibacterial or anticancer agent.

This work was supported by the Russian Science Foundation (project 19-75-10109).

### EP-TBS-86 Prediction of early bacterial activity (EBA) of bedaquiline in tuberculosis

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**Background:** The use of modelling and simulation offers the opportunity to establish the dose rationale for antitubercular drugs in humans based on the underlying pharmacokinetic-pharmacodynamic relationships, thereby ensuring exposures are achieved that correlate with efficacy (i.e., bactericidal and sterilizing activity). Recently, a semi-mechanistic two-state model was developed [1] to describe the antibacterial activity of rifampicin, which includes fast-(F) and slow-(S) growing subpopulations of *Mycobacterium tuberculosis*. Here we apply the same concepts to predict the early bactericidal activity (EBA) of bedaquiline (BDQ).

**Methods:** Using pharmacokinetic and CFU data from experimental protocols [2, 4], we have characterized the disposition and antibacterial effect of BDQ in mice. A previously developed bacterial growth dynamics model was implemented under the assumption of a theoretical maximum killing rate [1]. Parameters describing the antibacterial activity of BDQ were subsequently applied in conjunction with the predicted steady-state concentration in humans to predict EBA in patients. Simulation scenarios included a dose range from 50 to 500 mg/day. Results were compared to observed data in an EBA clinical trial including 68 tuberculosis patients.

**Results:** Model parameters describing the potency of BDQ indicate different effects on slow and fast-growing bacterial populations. Translation of the results to humans included the evaluation of pharmacokinetics at steady-state, with clearance and central volume of distribution estimates of 5.66L/h and 110L, respectively. Our mean model-predicted EBA were 0.031(0.080), 0.080(0.070), 0.083(0.061), and 0.116(0.090) log<sub>10</sub> CFU/

mL/day following doses of 100, 200, 300 and 400 mg/day, respectively. These findings are in agreement with observed mean EBA results reported in [3].

**Conclusions:** Whilst our approach confirms that 400mg dose achieves the greatest antibacterial effect, our results suggest that current dosing regimens may be optimised considering the long elimination half-life of BDQ. The use of a model-based framework may assist the dose rationale in early clinical development of novel antitubercular agents.



# Author Index

**Bold** indicates presenting author

## A

- A R. EP33-416-24  
 Aarnoutse R.E.  
 OA-07-543-21  
 Aartsma Y. OA-27-669-23  
 Abayneh S. OA-36-722-24  
 Abdunoor N. EP36-452-24  
 Abebe G. OA-38-740-24  
 Aben E. OA-38-736-24  
 Abhishek B. EP-TBS-11,  
 EP-TBS-12  
 Abiche T. EP37-460-24  
 Aboki D. OA-36-727-24  
 Abong J. EP19-278-22  
 Abongo T. OA-10-559-22,  
 OA-22-633-23  
 Aboot K. OA-06-537-21  
 Aboukhassib H.  
 OA-34-707-24  
 Abubakar S. OA-23-640-23  
 Abubakar S.I. EP14-235-22  
 Abubakar I. EP29-382-24  
 Abuko M. OA-06-537-21  
 Acevedo Mamani M.A.  
 EP14-232-22  
 Achebet S. OA-13-582-22  
 Acman M. OA-35-714-24  
 Acuna-Villaorduna C.  
 EP28-370-23  
 Adakun S. OA-14-590-22  
 Adams E. LB-2093-22  
 Adams J. EP02-110-21  
 Adamu A. OA-10-560-22,  
 OA-19-623-22, OA-36-  
 724-24, EP16-261-22,  
 EP17-268-22, **EP37-458-24**  
 Adamu H. OA-23-640-23,  
 EP32-412-24  
 Addo K.K. EP34-435-24,  
 EP-TBS-23, EP-TBS-44  
 Adejumo O. EP16-261-22  
 Adekambi T. EP-TBS-23  
 Adelakun O. **OA-34-709-24**  
 Adepu R. EP17-263-22  
 Adjobimey M. EP02-113-21,  
 EP23-319-23, EP23-322-23  
 Adnan S. OA-41-753-24  
 Aduh U. **EP12-216-22**  
 Affolabi D. EP19-283-22  
 Afonso C.F.F. EP01-101-21  
 Afrane A.K. EP-TBS-44  
 Agarwal A. **OA-19-619-22**  
 Agizew T. EP02-110-21  
 Agnarson M.A. **EP28-  
 371-23**  
 Agrawal N. EP30-387-24  
 Aguirre S. EP27-363-23  
 Agunwa C. **EP14-233-22**  
 Ahmad B. OA-41-749-24  
 Ahmad Khan F. LB-2047-21,  
 EP02-113-21  
 Ahmadu I. **OA-03-516-21**  
 Ahmadzada N. OA-41-  
 749-24  
 Ahmed S. OA-03-514-21,  
**OA-41-753-24,**  
**EP25-334-23**  
 Ahmed J.F. OA-34-710-24  
 Ahmed B. OA-36-722-24,  
 EP16-256-22  
 Ahmed A. **LB-2127-24**  
 Aia P. EP28-367-23  
 Aibana O. EP23-321-23  
 Akakimpa D. EP20-295-23  
 Akaniro O. EP08-172-21  
 A. Kendall E. OA-24-652-23  
 Akhgar M.H. EP21-306-23  
 Akinseye V. OA-34-709-24  
 Akkerman O. OA-24-648-23  
 Akmatova R. **EP05-144-21**  
 Akpodiete A. EP12-216-22  
 Akpomiemie O.  
 OA-36-727-24,  
 EP31-403-24  
 Akridge Abelman R.  
 OA-41-750-24  
 Aksenova V. EP-TBS-09,  
 EP-TBS-63  
 Akulov V. OA-04-525-21  
 Alacapa J. **EP05-146-21**  
 Alagna R. EP19-283-22  
 Alahi M.A. OA-41-748-24  
 Alamo M.L.T. EP23-319-23  
 Alba Montaña F.D.  
 EP14-232-22  
 Alebo A. OA-06-537-21  
 Alemu B. EP37-460-24  
 Aleu P. EP04-139-21,  
 EP30-390-24  
 Alexander K. EP04-130-21  
 Alexander M. EP27-357-23,  
**EP30-386-24**, EP-TBS-10,  
 EP-TBS-41  
 Alexandru S. EP05-151-21  
 Alferes de Lima D.  
**OA-03-517-21,**  
 EP34-429-24  
 Alffenaar J.-W.  
 OA-17-607-22,  
 EP34-430-24, EP-TBS-59  
 Alffenaar J. OA-24-648-23  
 Alffenaar J.W. EP27-363-23,  
 EP-TBS-76  
 Alghamdi W. TBS-OA-09  
 Ali S. OA-37-734-24  
 Ali N. EP-TBS-37  
 Alisjahbana B. TBS-OA-01  
 Aliyu I. EP06-156-21  
 Alkazi A.M. **OA-21-627-22**  
 Allender C. OA-35-717-24  
 Alphonsus C.  
 OA-23-642-23,  
**EP07-166-21,**  
 EP12-209-22,  
 EP14-233-22,  
**EP37-461-24**  
 Alsadig H. EP24-328-23  
 Al-Shaer M. OA-37-729-24  
 Altaf R. **EP25-338-23**  
 Altamirano E. EP12-211-22  
 Alva S. EP13-221-22  
 Alvarez C. OA-24-654-23  
 Alves Y. EP19-282-22  
 Alves Y.M. EP36-446-24  
 Alwi B. EP01-108-21  
 Alyushin S. EP29-383-24  
 Ama C. OA-35-717-24  
 Amalia B. **EP35-439-24**  
 Amanullah F. OA-34-710-24  
 Ameal C. TBS-OA-02  
 Amico R. OA-06-540-21  
 Amico K.R. OA-12-573-22  
 Amisi J. OA-02-511-21  
 Amuasi J.H. EP31-397-24  
 Amuge P. EP18-275-22  
 Anaedobe I. EP19-281-22,  
 EP34-433-24  
 Anaman J. OA-07-546-21,  
 EP05-142-21  
 Anand S. EP26-344-23,  
 EP26-347-23  
 Anandita Y. EP01-108-21  
 Ananthakrishnan R.  
 OA-21-629-22,  
 EP14-237-22,  
 EP33-417-24  
 Andama A. OA-11-565-22,  
 OA-38-736-24,  
 OA-38-738-24,  
 EP36-449-24  
 Anderson S. OA-27-667-23,  
 EP29-382-24  
 Andrade H. EP04-130-21  
 Andrade H.L. EP36-446-24  
 Andrade B. EP-TBS-10,  
 EP-TBS-41  
 Andrade B.B. EP-TBS-15  
 Andre E. OA-23-645-23  
 Andreevskaya S.  
 OA-11-567-22  
 Andres S. EP-TBS-50,  
 EP-TBS-53  
 Angala P. OA-02-511-21,  
 OA-21-630-22  
 Angappan S.K. EP07-161-21  
 Angero B. OA-06-537-21  
 Anglaret X. OA-01-503-21  
 Angodo M. OA-06-537-21  
 Anh D.D. OA-36-726-24,  
 EP31-399-24  
 Anh N. EP10-190-21  
 Anh E. EP-TBS-27  
 Anil S. EP33-416-24  
 Ansari M.S. EP37-462-24  
 Anshambi N. **EP-TBS-54**  
 Anthwal D. EP-TBS-42  
 Antia E. EP11-199-22  
 Antiparra R. OA-05-533-21  
 Antonenka U. EP36-453-24  
 Antwi-Baffour S. EP-TBS-23  
 Anumba J. EP04-135-21  
 Anyim M. OA-23-642-23,  
 EP12-209-22,  
 EP14-233-22,  
 EP37-461-24  
 Anzures E. EP07-164-21  
 Aparecida Araújo  
 Cardoso C. EP-TBS-19  
 Apaza Miranda A.  
 EP14-232-22  
 Apolisi I. EP17-266-22  
 Apollo T. OA-09-552-21  
 Aquino A.C. EP19-278-22  
 Aragaw S. EP18-277-22  
 Aralov A. EP-TBS-85  
 Arao R.M. **EP05-150-21**  
 Arbiv O.A. **OA-07-542-21**  
 Arcêncio R. **EP01-101-21,**  
**EP04-130-21,**  
**EP04-137-21,**  
**EP19-282-22**  
 Arcêncio R.A. **EP36-446-24**  
 Arenivas A. EP12-208-22  
 Arinaitwe M. **OA-09-550-21**  
 Arinaminpathy N.  
 EP28-372-23  
 Arinola G. EP-TBS-05  
 Armitage E. EP-TBS-29  
 Armstrong D. EP-TBS-52  
 Armstrong-Hough M.  
 OA-12-572-22  
 Arrazola de Onate W.  
 OA-04-524-21  
 Arroyo L.H. EP01-101-21,  
 EP36-446-24  
 Arroyo L. EP04-130-21  
 Arscott-Mills T.  
 OA-03-515-21,  
 EP25-337-23  
 Artawan Eka Putra I.W.G.  
**OA-33-702-24**  
 Asadi L. OA-07-542-21  
 Asege L. EP36-449-24  
 Ashaba J. EP36-452-24  
 Aspden M. LB-2110-24  
 Assebe L.F. **EP28-369-23**

- Astuti P.A.S. OA-33-702-24  
 Ataula Khan S.  
 OA-10-556-22  
 Atobatele A. OA-10-560-22,  
 OA-36-724-24  
 Atkins S. EP13-225-22  
 Atwine D. EP02-110-21  
 Audo M. EP11-204-22  
 Audrey W. EP01-108-21  
 Augustin M. EP-TBS-07  
 Aung W.W. OA-35-720-24  
 Aung S.T. EP09-185-21  
 Aung W.Y. EP19-279-22  
 Aung Y.K. EP30-391-24  
 Aung H.K.K. EP33-421-24  
 Avaku I. EP18-277-22  
 Avaliani Z. OA-40-742-24,  
 TBS-OA-09, EP-TBS-49  
 Avsar K. TBS-OA-04  
 Awalime D. **EP05-142-21**  
 Awe A. OA-02-507-21,  
 OA-14-589-22,  
 OA-23-640-23,  
 EP08-172-21,  
 EP12-216-22,  
 EP13-222-22,  
 EP14-235-22,  
 EP22-312-22,  
 EP30-392-24,  
 EP32-412-24  
 Awosika-olumo A.  
 EP06-152-21  
 Ayakaka I. OA-03-521-21  
 Ayala D. LB-2110-24  
 Ayalneh H. EP18-277-22  
 Ayles H. EP20-290-23  
 Ayoubi M.K. OA-16-602-22  
 Ayoubi K. OA-41-749-24
- B**  
 Ba T.A. EP07-165-21  
 Baabe N. EP18-277-22  
 BabaMaiyaki M.  
 EP06-156-21  
 Babawale V. EP09-179-21  
 Babawale A. EP32-412-24  
 Babayi A. EP13-222-22,  
**EP32-412-24**  
 Bablishvili N. TBS-OA-09,  
 EP-TBS-49  
 Babu S. EP27-357-23  
 Bachmann T. EP-TBS-61  
 Badalato N. EP-TBS-53  
 Baddeley A. EP18-271-22  
 Badje A. OA-01-503-21  
 Bae S.-H. EP22-313-23  
 Bagnoli J. EP-TBS-52  
 Bah B. EP02-110-21  
 Bahr N.S. LB-1968-21  
 Bai H. EP08-170-21  
 Baibek A. **OA-11-567-22**  
 Baik Y. **OA-02-509-21**,  
 OA-31-689-23,  
 EP06-157-21  
 Baisley K. OA-17-609-22,  
 EP32-410-24  
 Bajehson M. **EP06-156-21**,  
 EP09-179-21, EP19-286-22
- Bakuli A. OA-03-519-21,  
 OA-35-713-24,  
 OA-40-743-24,  
 EP25-342-23  
 Balaji S. OA-34-711-24  
 Balaji S. EP01-100-21  
 Balanag V. EP01-103-21  
 Balasubramanian D.  
**EP05-143-21**,  
 EP07-161-21,  
**EP32-413-24, EP33-423-24**  
 Baleeta K. OA-15-595-22,  
 OA-18-616-22  
 Balgeman A. TBS-OA-02  
 Baliashvili D. EP29-378-24  
 Balloux F. OA-35-714-24  
 Banay R. EP33-414-24  
 Banda C. OA-10-558-22  
 Banda L. OA-34-712-24  
 Bangdiwala A.S.  
 LB-1968-21  
 Bangoura A.M.  
 EP13-220-22  
 Banu P. EP-TBS-47  
 Banzakadilo C.  
 OA-01-500-21,  
**OA-37-730-24**  
 Bao Z. EP-TBS-59  
 Baqui A.H. OA-03-514-21  
 Baqui A. EP25-334-23  
 Barasa E. EP16-254-22  
 Barbakadze K. TBS-OA-09  
 Barcellos M. OA-29-685-23,  
 EP16-259-22  
 Barilar I. EP-TBS-50  
 Barnabas R. OA-01-503-21  
 Baron V. OA-25-659-23  
 Barrameda A.J.  
 EP19-278-22  
 Barrameda M. EP30-393-24  
 Barreto-Duarte B.  
 EP-TBS-10  
 Baruwa E. OA-10-560-22,  
 OA-19-623-22,  
 OA-36-724-24,  
 EP16-261-22,  
 EP17-268-22,  
 EP37-456-24,  
 EP37-458-24  
 Bascuna J.E. EP16-262-22  
 Basher M.A.K. EP08-168-21,  
**EP17-264-22, EP37-457-24**  
 Basingnaa A. EP-TBS-23  
 Basnet R. EP07-163-21  
 Bassett J. OA-28-677-23  
 Bastard M. EP-TBS-80  
 Bathi Siddappa P.  
 OA-06-536-21  
 Batist E. OA-02-513-21  
 Battaglia A. EP27-363-23  
 Beard J. EP25-339-23  
 Beardsley J. OA-36-726-24,  
 EP31-399-24  
 Becerra M. OA-34-710-24,  
 EP04-134-21,  
 EP09-180-21,  
 EP14-234-22,  
 EP23-320-23  
 Becerra M.C. EP34-426-24
- Beckhorn C. EP12-211-22  
 Begum I. EP17-264-22  
 Begum R. EP33-415-24  
 Behara I. OA-18-612-22  
 Bei C. **EP11-205-22**  
 Bejaoui S. EP36-450-24  
 Bekker A. OA-41-752-24  
 Beko B. EP17-265-22  
 Belilovskiy E. **EP13-223-22**  
 Belinga E. OA-13-579-22  
 Bello G.L. EP-TBS-37  
 Belskih A. EP-TBS-72  
 Benedetti A. LB-2047-21  
 Benedicto E. EP28-371-23  
 Benson U. EP32-405-24  
 Berger C. OA-13-580-22,  
 OA-18-613-22,  
 OA-35-717-24  
 Berger M. EP-TBS-07  
 Berhanu R. **OA-23-646-23**  
 Berido C. OA-24-654-23  
 Bern H. OA-17-608-22  
 Bernachea M.P.  
 EP22-311-23  
 Bernays S. OA-36-726-24,  
 EP31-399-24  
 Berra T. EP04-130-21,  
 EP19-282-22  
 Berra T.Z. EP36-446-24  
 Berrada J. OA-34-707-24  
 Bespyatykh J. EP-TBS-85  
 Bethrand O. EP06-156-21  
 Beukes A. **OA-16-604-22**,  
 EP19-284-22  
 Beutler M. **EP36-453-24**  
 Bezerra A.L. EP16-259-22  
 Bhandari H. EP28-371-23  
 Bharathiraja T. EP01-100-21  
 Bhardwaj M. **EP15-247-22**,  
 EP26-350-23, EP37-462-24  
 Bhargava S. OA-16-598-22  
 Bhattachan A. EP07-163-21  
 Bhattraï R. EP07-163-21,  
 EP07-163-21  
 Bhide S. EP21-302-23  
 Bhide P. EP28-365-23  
 Bhosale R. EP27-357-23,  
 EP30-386-24, EP-TBS-10,  
 EP-TBS-41  
 Biagini G. OA-37-733-24  
 Biao X. EP34-430-24  
 Biermann O. EP13-225-22  
 Billieux V. OA-03-514-21  
 Birabwa E. OA-13-582-22  
 Biraro S. OA-12-571-22  
 Birembano F. OA-23-645-23  
 Birjovanu G. EP03-119-21  
 Bissell K. OA-03-520-21  
 Black D. OA-01-506-21  
 Black J. OA-09-554-21,  
 OA-37-732-24,  
 EP01-109-21,  
 EP05-148-21  
 Blank H.-P. OA-27-670-23  
 Blumberg H. OA-27-672-23,  
 OA-40-742-24,  
 EP29-378-24  
 Boakye A.N. **EP-TBS-23**  
 Bocanera R. OA-09-552-21
- Bodolo J. EP26-346-23  
 Boehme C. OA-16-600-22  
 Boeree M.J. OA-07-543-21,  
 OA-35-713-24  
 Boeree M. OA-25-659-23,  
 TBS-OA-14, EP34-429-24,  
 EP34-432-24  
 Boerema S. **EP29-381-24**  
 Boffa J. OA-10-557-22,  
**OA-22-635-23**,  
 OA-22-638-23,  
 OA-22-639-23  
 Bogati H. EP05-144-21  
 Bogdanov A.  
 OA-04-523-21,  
 OA-04-526-21  
 Bohlela N. EP01-104-21  
 Boiditswe S. OA-03-515-21,  
 EP25-337-23  
 Boitor O. LB-2047-21  
 Bollela V.R. EP01-101-21  
 Bonfoh B. EP-TBS-44  
 Bonnet M. OA-41-750-24,  
 EP12-215-22  
 Boodhram R. OA-06-540-21,  
 OA-12-573-22  
 Boonathapun N.  
 EP33-421-24  
 Boonyasopun J. EP-TBS-31  
 Bor J. EP01-102-21  
 Borand L. EP18-272-22,  
 EP33-425-24  
 Borant L. EP12-215-22  
 Borges J. EP-TBS-24  
 Borhade A. OA-26-662-23  
 Borisov S. EP13-223-22  
 Bornefall A. OA-17-607-22  
 Borrell S. OA-27-672-23  
 Böttger E.C. OA-13-581-22,  
 OA-35-716-24  
 Boule A. EP04-129-21,  
 EP04-131-21  
 Boulware D.R. LB-1968-21  
 Bouslikhane M.  
 OA-34-707-24  
 Boutachkourt F.  
 OA-23-645-23  
 Bouton T. EP01-102-21  
 Bouton T.C. **EP09-177-21**,  
**EP22-318-23**  
 Bouzouita I. **EP36-450-24**  
 Bovana S. EP07-167-21  
 Boyanapalli R. EP-TBS-43  
 Boyd A.T. EP18-277-22  
 Boyle D. OA-05-530-21  
 Boyles T.H. EP03-119-21  
 Bozzani F. EP28-374-23  
 Bradley M. OA-11-567-22,  
 EP19-287-22  
 Brambilla D. OA-05-529-21  
 Branigan D. **EP10-196-21**  
 Breton G. EP12-215-22  
 Brey Z. OA-23-646-23  
 Briggs-Hagen M.  
 EP22-307-23  
 Brightman H.  
 OA-13-583-22,  
 OA-13-584-22,  
 EP01-106-21



- Britton W. **EP-TBS-29**  
 Brodhun B. EP29-376-24  
 Broger T. **EP-TBS-38**  
 Bronson G. EP02-111-21  
 Brooks M. **OA-34-710-24**,  
 EP04-134-21,  
**EP14-234-22**,  
**EP23-320-23**  
 Brooks M.B. OA-37-734-24,  
 EP34-426-24  
 Brostrom R. EP07-164-21  
 Brouwer M. **EP26-350-23**  
 Brown J. OA-09-550-21  
 Bruce A. EP19-282-22  
 Bruce A.T.I. EP36-446-24  
 Bruchfeld J. OA-17-607-22,  
 EP34-430-24, EP-TBS-59  
 Brudney K. OA-28-678-23  
 Bryant K. EP02-115-21  
 Bryden W. TBS-OA-08  
 Brynildsrud O.  
 OA-35-714-24  
 BS P. OA-06-536-21  
 Bu K. EP-TBS-33  
 Buhay H. EP30-393-24  
 Bulti A.B. **OA-24-653-23**  
 Bundi S. **OA-16-601-22**  
 Bunga S. EP18-277-22  
 Buregyeya E. OA-09-551-21  
 Burnett J.M. EP20-290-23  
 Burton A. OA-32-698-24  
 Burua A. **EP30-390-24**  
 Burzynski J. **OA-26-665-23**,  
**OA-26-666-23**,  
 EP26-352-23  
 Busulwa P. **EP18-269-22**  
 Buthelezi S. OA-24-653-23  
 Butler C. OA-12-569-22,  
 OA-12-574-22  
 Butov D. **OA-19-622-22**  
 Butova T. OA-19-622-22  
 Buu T. EP10-190-21  
 Byaruhanga R.  
 OA-15-592-22,  
 EP30-390-24  
 Byashalira K. **OA-24-650-23**
- C**  
 Cabello-Pasini A. EP-TBS-83  
 Caceres-Nakiche T.  
 EP-TBS-38  
 Cadmus S. OA-34-709-24  
 Cai Y. EP09-182-21  
 Cain K. EP11-206-22  
 Calatroni A. OA-17-610-22  
 Calçada Carvalho A.C.  
 OA-29-685-23,  
 EP16-259-22  
 Calderon R. LB-2122-22  
 Calderón R.I. OA-33-703-24  
 Calderón R. EP-TBS-02  
 Calderon Espinoza R.  
 EP34-426-24  
 Caleb Erisa K. **OA-24-652-23**  
 Call C. TBS-OA-08  
 Campbell C.N.J.  
 OA-04-522-21  
 Campbell J.R. OA-07-542-21  
 Campbell C. OA-27-667-23  
 Campbell J. **EP18-272-22**  
 Campos-Olivas R.  
 OA-05-532-21  
 Canagasabay D.  
 OA-01-500-21,  
 OA-37-730-24  
 Cancino-Muñoz I.  
 LB-2082-21  
 Cantera J. **OA-05-530-21**  
 Cao-Hung T. OA-36-723-24  
 Capeding T.P.J.Z.  
 EP28-364-23  
 Cariem R. EP17-266-22  
 Carla Felix Manuel Y.  
 OA-07-546-21  
 Carmona S. OA-38-741-24,  
 LB-2093-22  
 Carney T. OA-32-697-24,  
 EP22-318-23  
 Carter E.J. OA-02-511-21  
 Casenghi M. OA-02-510-21,  
 OA-02-512-21,  
 OA-23-643-23,  
 OA-41-747-24,  
 OA-41-750-24,  
 EP07-159-21,  
 EP07-160-21,  
 EP07-161-21  
 Castell S. EP31-397-24  
 Castellanos M.E.  
 OA-15-597-22  
 Castellanos Reynosa M.E.  
**OA-26-661-23**  
 Castelnuovo B. EP13-224-22  
 Castro K. OA-09-551-21,  
 EP13-221-22  
 Castro M. OA-18-615-22  
 Castro M.C. OA-24-654-23,  
 EP11-202-22  
 Cattamanchi A.  
 OA-11-565-22,  
 OA-13-580-22,  
 OA-18-613-22,  
 OA-31-689-23,  
 OA-35-717-24,  
 OA-38-736-24,  
 OA-38-738-24,  
**LB-2087-24**,  
 EP13-219-22,  
 EP13-224-22,  
 EP13-226-22,  
 EP15-248-22,  
 EP36-449-24  
 Caws M. OA-31-690-23,  
 EP13-225-22  
 Centner C. EP09-176-21  
 Cevik M. **OA-24-648-23**  
 Chabala C. LB-2056-24,  
 EP02-114-21,  
 EP23-323-23  
 Chadha S. OA-16-598-22  
 Chadha S. OA-16-600-22,  
 EP37-455-24,  
 EP37-464-24  
 Chadyiwa M. EP21-304-23  
 Chafulumira H.  
 EP14-231-22,  
 EP14-236-22  
 Chaisson R. OA-15-594-22  
 Chaisson L. **EP36-449-24**  
 Chakare T. **EP24-329-23**  
 Chakaya Muhwa J.  
 EP24-331-23  
 Chakhaia T. EP29-378-24  
 Chakraborti A. EP09-184-21  
 Chan T.-H. **OA-25-656-23**,  
 EP06-154-21  
 Chan H.-H. OA-35-715-24  
 Chan P.-C. **EP06-154-21**,  
**EP22-309-23**  
 Chan P.C. EP10-188-21  
 Chandra S. EP31-398-24  
 Chandrasekaran P.  
 EP-TBS-47  
 Chang R. OA-22-634-23,  
 EP16-260-22,  
 EP20-296-23  
 Chang C.L. OA-35-720-24  
 Chang V. **TBS-OA-15**,  
 EP-TBS-73  
 Charalambous S.  
 OA-40-743-24,  
 EP22-315-23, EP-TBS-11,  
 EP-TBS-12  
 Charlet D. EP01-106-21  
 Chatterjee S. **EP28-365-23**  
 Chauffour J. OA-09-551-21  
 Chauhan A. OA-16-600-22  
 Chauhan L. EP12-214-22  
 Chawla A. EP30-387-24  
 Chay S. EP18-272-22  
 Chebon H. OA-10-559-22  
 Checkley W. OA-03-514-21,  
 EP07-162-21  
 Chegou N.N. LB-2092-21  
 Cheikh N. EP28-375-23  
 Chelvi S. OA-34-711-24  
 Chen X. OA-09-555-21,  
 EP09-182-21  
 Chen J. LB-2070-24  
 Chen S. EP09-183-21  
 Chen L. EP10-195-21  
 Chen H. EP22-316-23  
 Chen N. EP22-316-23  
 Chen C.-Y. **EP29-380-24**  
 Chenciner L. **OA-31-693-23**  
 Chendi B.H. **LB-2092-21**  
 Cheng M.-H. OA-07-548-21  
 Cheng S. LB-2070-24  
 Cherif G.-F. EP13-220-22  
 Chernousova L.  
 OA-11-567-22  
 Cheyip M. OA-01-502-21,  
 OA-01-505-21  
 Chiacchiaretta M.  
 TBS-OA-11  
 Chiang S. EP12-211-22,  
**EP23-321-23**  
 Chijioke Akaniro O.  
 EP06-152-21  
 Chijioke-Akaniro O.  
 EP12-216-22, **EP18-273-22**  
 Chikamatsu K. EP-TBS-38  
 Chikovore J. OA-10-557-22,  
 OA-22-635-23,  
 OA-22-638-23,  
**OA-22-639-23**  
 Chiliade P. EP22-307-23  
 Chilukutu L. LB-1903-23,  
**EP36-454-24**  
 Chimatiro D. EP14-230-22,  
 EP14-238-22  
 Chimpeni A. **EP03-126-21**  
 Chimunhu C. EP21-299-23  
 Chimzizi R. OA-25-657-23,  
 EP06-158-21,  
 EP21-303-23,  
 EP23-323-23,  
 EP30-388-24  
 Chincharauli M.  
 EP29-378-24  
 Chiner-Oms Á. EP-TBS-51  
 Chingombe I.  
 OA-09-552-21  
 Chinoko B. OA-40-744-24  
 Chipato W.E. **EP-TBS-75**  
 Chirehwa M. EP09-176-21  
 Chirico C. EP05-145-21,  
 EP22-311-23  
 Chisenga T. EP06-158-21,  
 EP21-303-23  
 Chittamany P. EP20-296-23,  
 EP28-366-23  
 Chittiboyina S.  
**EP17-263-22**  
 Chiume L. LB-2112-24,  
 EP03-120-21  
 Chiviya W. EP33-419-24  
 Chiwenkha P. **EP15-240-22**,  
 EP15-242-22,  
 EP15-243-22  
 Cho Y.-S. EP-TBS-77,  
 EP-TBS-78, EP-TBS-79  
 Choi K. LB-2127-24  
 Choi Y.-K. EP-TBS-78  
 Chong I.-W. OA-07-548-21  
 Chongsuvivatwong V.  
 EP21-297-23  
 Choo L. EP02-114-21  
 Chopra K.K. EP26-347-23,  
**EP31-398-24**  
 Chorn S. EP33-425-24  
 Chowdhury N.  
 OA-03-514-21  
 Christensen D.  
 OA-24-650-23  
 Chry M. **OA-23-641-23**  
 Chu A.L. **OA-33-703-24**  
 Chu P.W. EP10-188-21  
 Chuck C. EP26-352-23  
 Chukwu J. OA-23-642-23,  
 EP12-209-22  
 Chukwu J.N. EP07-166-21,  
 EP14-233-22,  
 EP37-461-24  
 Chukwueme N.C.  
 EP06-152-21  
 Chukwulobelu U.  
 OA-14-589-22,  
 OA-23-644-23,  
 EP04-135-21,  
 EP13-222-22,  
 EP20-289-23,  
 EP24-325-23,  
 EP30-392-24,  
 EP31-402-24

- Chukwuogo O.  
**OA-10-561-22**,  
 OA-14-588-22,  
**OA-16-603-22**,  
 EP06-156-21,  
 EP19-286-22,  
 EP26-348-23,  
 EP30-385-24,  
 EP31-394-24,  
**EP32-406-24**,  
 EP32-409-24
- Chumburidze N.  
 OA-40-742-24
- Chun H. EP18-277-22
- Chungu C. **EP23-323-23**,  
 EP30-388-24
- Chura R. LB-2122-22
- Churchyard G.  
 OA-07-546-21,  
 OA-40-743-24,  
 EP28-368-23
- Ciccacci F. **OA-05-529-21**
- Cikobe V. OA-01-500-21
- Ciobanu A. EP05-151-21
- Cirillo D. OA-28-673-23,  
 LB-2100-22, EP19-283-22
- Cirillo D.M. TBS-OA-11
- Cisse D. EP13-220-22
- Clark R.A. **EP06-155-21**
- Clarke A. OA-04-522-21
- Clarkson M. **EP28-373-23**
- Claxton P. OA-03-517-21
- Clemente J. EP-TBS-33
- Clewe O. EP27-354-23
- Click E. EP11-206-22
- Coarfa C. EP-TBS-06
- Cobelens F.G. EP11-201-22
- Cobelens F. EP-TBS-64
- Codlin A.J. OA-07-547-21,  
 OA-28-674-23,  
 EP10-194-21,  
 EP16-257-22,  
 EP31-396-24
- Coggin W. EP22-307-23
- Cohen T. OA-11-566-22,  
 OA-32-694-24
- Cohn J. OA-02-510-21,  
 OA-02-512-21,  
 OA-23-643-23,  
 OA-41-747-24,  
 OA-41-750-24,  
 EP07-159-21,  
 EP07-160-21,  
 EP07-161-21
- Cohn S. OA-15-594-22
- Coit J. EP12-211-22
- Colbourn T. OA-03-514-21,  
 EP25-339-23
- Collin S. EP29-382-24
- Colvin C. OA-09-551-21,  
 EP13-221-22
- Comas I. LB-2082-21,  
 EP-TBS-49, EP-TBS-51
- Comella-del-Barrio P.  
**OA-05-532-21**,  
**EP27-355-23**
- Comhaire L. OA-04-524-21
- Congdon M. OA-03-515-21
- Conradie F. OA-17-610-22
- Conroy O. EP29-382-24
- Conteh O. EP-TBS-53
- Contreras C.C. OA-33-703-24
- Contreras C. EP-TBS-02
- Cookson S. OA-32-698-24
- Cooray P. **OA-33-701-24**
- Corbett E. LB-2112-24,  
 EP03-120-21, EP-TBS-40
- Cordon O. EP06-157-21
- Coronel J. OA-35-719-24
- Costa A.D.T. **EP-TBS-37**
- Cotton S. **EP36-451-24**
- Court R. **EP09-176-21**
- Coutisson S. OA-41-753-24
- Couto Sant'Anna C.  
 EP-TBS-19
- Cowan J. OA-28-678-23
- Cox H. OA-09-554-21,  
 EP01-109-21,  
 EP05-148-21
- Cox V. OA-13-577-22,  
 OA-15-593-22,  
 EP05-147-21,  
 EP12-217-22
- Cox S. OA-18-615-22
- Cox S.E. OA-24-654-23,  
 OA-37-728-24,  
 LB-2071-23, EP11-202-22
- Coxon C. LB-2110-24
- Crampin A. OA-34-712-24
- Cranmer L. OA-01-501-21
- Cresswell F.V. LB-1968-21
- Cresswell J. EP21-298-23
- Creswell J. EP16-251-22,  
 EP34-428-24
- Crispim J.d.A. EP01-101-21
- Crispim J. EP04-130-21,  
 EP19-282-22
- Crispim J.A. EP36-446-24
- Crook A.M. LB-2056-24,  
 EP02-112-21
- Crowder R. OA-13-580-22,  
 OA-18-613-22,  
**OA-35-717-24**
- Croxatto A. LB-2100-22
- Crudu V. OA-38-737-24
- Cruz A. OA-31-692-23,  
 EP23-321-23
- Cuevas L.E. OA-05-532-21,  
 EP27-355-23
- Cunnama L. EP16-254-22
- Cunningham C.K.  
 EP25-337-23
- D**
- Dadu A. EP05-151-21
- Daftary A. OA-06-540-21,  
 OA-10-557-22,  
**OA-12-573-22**,  
 OA-22-635-23,  
 OA-22-638-23,  
 OA-22-639-23,  
 EP33-418-24
- Dalal A. EP01-105-21
- Dalay V. EP19-278-22
- Dale K.D. TBS-OA-07
- Dam T. EP16-257-22,  
 EP31-396-24
- Dambe I. EP14-231-22,  
 EP14-236-22,  
 EP14-238-22
- Dang H.M.T. OA-28-674-23
- Dang T. **OA-36-723-24**
- Daniel S. EP12-214-22
- Daniel de Aquino E.  
 OA-29-685-23,  
 EP16-259-22
- Daniels B. OA-10-557-22,  
 OA-22-635-23,  
 OA-22-638-23
- Daniels J. LB-2090-22,  
**EP07-167-21**
- Dara M. OA-04-525-21,  
 OA-04-528-21,  
 EP01-107-21
- Darie Y. EP37-460-24
- Darrah T. TBS-OA-02
- Dartois V. EP-TBS-81
- Darvell M. OA-04-522-21
- Das M. EP01-105-21,  
 EP33-418-24
- Das C. EP32-413-24
- Dasari R. OA-06-536-21,  
 EP31-395-24, EP31-401-24
- Da Silva P. OA-16-599-22
- da Silva Corrêa R.  
 EP-TBS-16, **EP-TBS-24**
- da Silva Rezende Moreira A.  
**OA-29-685-23**,  
**EP16-259-22**
- Dass M. **EP-TBS-42**
- Date A. EP21-302-23
- Datta B. OA-21-627-22
- Dauda Samuel H.  
 OA-03-516-21
- David A. OA-38-741-24
- Davies Forsman L.  
**EP34-430-24**, EP-TBS-59
- Davis N. **OA-09-551-21**,  
 EP13-221-22
- Davis J.L. OA-12-572-22,  
 OA-28-679-23,  
 LB-2087-24
- Dayi N. EP32-410-24
- Dear J. EP-TBS-61
- Deborggraeve S.  
**OA-29-686-23**
- De Campo J. EP07-162-21
- de Castro B.R.  
 OA-26-665-23
- Degrugy K. OA-16-601-22
- Dequ D. EP32-411-24
- Dejene S. OA-09-551-21
- De Jong B. EP19-283-22
- Dekkers B. OA-24-648-23
- Dela Rosa J.A. EP28-364-23
- della Pasqua O.  
 EP02-117-21
- Della Pasqua O. EP-TBS-86
- Demarco R. EP08-172-21
- Den Boon S. **EP18-271-22**
- Dendukuri N. EP19-285-22
- de Neeling H.  
 OA-32-695-24
- Deng G. OA-05-535-21,  
 EP09-182-21
- Denholm J.T. TBS-OA-07
- Denkinger C. OA-28-673-23,  
 OA-38-741-24,  
 LB-2093-22
- Denkinger C.M.  
 OA-38-735-24,  
 OA-38-737-24, EP-TBS-38
- Denoeud-Ndam L.  
 OA-02-508-21,  
**OA-02-510-21**
- Denti P. OA-41-752-24,  
 EP09-176-21
- de Paula Martins C.  
 EP-TBS-19
- Der J. OA-17-609-22
- Derendinger B. **TBS-OA-10**
- Desano C. OA-36-721-24
- Deshmukh R. EP21-302-23
- Deshpande M. EP15-249-22
- De Souza-Galvão M.L.  
 EP-TBS-03
- Destura R. OA-13-580-22,  
 OA-35-717-24
- Detjen A. OA-41-751-24,  
 EP12-213-22
- Dev P. OA-25-655-23
- de Villiers A. **EP24-332-23**
- de Vos M. **OA-38-741-24**,  
 EP09-177-21
- DeVosh M. LB-2100-22
- de Vries N. EP09-176-21
- de Vries G. **EP29-377-24**,  
 EP29-382-24
- De Vries G. EP11-198-22
- Dewan R.K. EP-TBS-39
- Dewi K.R.A. OA-33-702-24
- de Wit L. EP10-193-21,  
 EP29-381-24
- Deya R. **EP24-331-23**
- Dhaliwal K. EP-TBS-61
- Dhasmana D.J.  
 OA-03-517-21
- Dhawale A. OA-26-663-23
- Dheda K. OA-17-610-22
- Dhillon J. EP02-110-21
- Dhir A. EP28-371-23
- Diacon A. OA-17-610-22,  
 EP-TBS-33
- Diallo A. EP07-165-21,  
**EP15-246-22**
- Diallo B. EP15-246-22
- Dian S. TBS-OA-01
- Dias I. EP35-441-24,  
 EP35-442-24,  
 EP35-443-24,  
 EP35-444-24
- Diaz N. OA-06-539-21
- Diaz G. OA-28-679-23
- Dickson-Hall L.  
**OA-09-554-21**,  
 EP05-148-21
- Didelot X. OA-35-714-24
- Didik V.S. EP29-380-24
- Diero L. EP11-203-22
- Dikko A. EP06-156-21,  
 EP19-286-22
- Dil S. EP08-171-21
- Dildar M.Z. OA-16-602-22
- Dillingham R. EP11-197-22
- Dim B. EP18-272-22

- Dimba A. OA-10-558-22  
 DiNardo A. TBS-OA-04,  
**EP-TBS-06**  
 Dineshkumar P.  
 EP35-443-24,  
 EP35-444-24  
 Dini S. **EP35-437-24**,  
**EP35-440-24**  
 Dinkele R. TBS-OA-08  
 Dioukhane E. EP15-246-22  
 Divala T. **LB-2112-24**  
 Dizha I. OA-14-591-22  
 Dlamini S. EP23-324-23  
 Dlamini P.S. EP33-419-24  
 Dlamini Q. EP-TBS-06  
 Dobaño C. LB-2100-22  
 Dobrikov G. EP34-434-24  
 Dodd P. EP-TBS-40  
 Dogonadze M. EP34-434-24  
 Dolby T. EP01-102-21  
 Doltu S. **EP05-151-21**  
 Dolynska M. EP23-321-23  
 Domaszewska T.  
 OA-27-670-23,  
**EP29-376-24**  
 Dombay E. **OA-25-659-23**,  
 TBS-OA-14, **EP34-429-24**,  
 EP34-432-24  
 Domínguez J.  
 OA-05-532-21,  
 EP27-355-23, EP-TBS-03  
 Dominic N. EP03-122-21  
 Donchuk D. EP29-380-24  
 Dong T.T.T. **OA-07-547-21**,  
**EP10-194-21**  
 Dong C. EP16-251-22  
 Donkor S. EP-TBS-11,  
 EP-TBS-12  
 Donnellan S. **OA-37-733-24**  
 Donsa L. OA-10-558-22  
 Dooley K.E. EP12-208-22  
 do Rosário Delgado Nunes  
 de Serpa C. EP04-137-21  
 dos Santos Fernandes  
 Lara C. OA-29-685-23,  
 EP16-259-22  
 dos Santos Lima I.C.  
 EP16-259-22  
 Douglas-Jones B.  
 LB-2090-22, EP17-266-22  
 Dowdy D. OA-02-509-21,  
 OA-31-689-23,  
 LB-2087-24, EP06-157-21,  
 EP16-251-22,  
 EP36-449-24  
 Dragos-Cosmin Z.  
 OA-35-718-24  
 Drain P.K. OA-05-531-21  
 Draoui H. EP36-450-24  
 Draper H.R. OA-17-611-22  
 Drexler J.-F. LB-2093-22  
 Dreyer V. **OA-25-655-23**,  
 EP-TBS-50  
 Du Y. EP13-229-22  
 Duana I.M.K. OA-33-702-24  
 Dube G.S. EP22-308-23  
 du Cros P. OA-38-735-24  
 Dudek M.M. LB-2110-24  
 Dugyala R.R. EP07-161-21  
 Duka M. EP29-380-24  
 Dumicho A.Y.  
 OA-24-653-23  
 Dunbar R. OA-21-632-22,  
 EP04-129-21, EP23-324-23  
 Dung N.C. EP-TBS-77  
 Duong L. OA-12-576-22  
 Du Preez K. OA-28-675-23,  
**EP23-324-23**  
 Durbin D. TBS-OA-12  
 Dushime A. EP05-140-21  
 Dusthacker A.  
 OA-11-568-22  
 Dutta T. EP03-127-21,  
 EP05-141-21  
 Dutta P. EP-TBS-70  
 Dwilow R. **EP07-164-21**  
 Dye C. EP24-332-23  
 Dyrhol-Riise A.M.  
 LB-2092-21
- E**  
 Eang M.T. EP18-272-22  
 Easow Mathew M.  
**EP03-127-21**, EP05-141-21  
 Ebenezer R.S.  
 OA-11-568-22  
 Eddyani M. EP19-283-22  
 Edem V. **EP-TBS-05**  
 Edwards T. LB-2071-23,  
 EP11-202-22  
 Egbule D. OA-36-727-24,  
 EP24-333-23, **EP32-407-24**  
 Egbule1 D. EP31-403-24  
 Egger M. OA-13-581-22,  
 OA-35-716-24  
 Eggo R. OA-14-585-22  
 Eholie S. OA-01-503-21  
 Ehrlich R. OA-12-569-22,  
 OA-12-574-22  
 Eisenhut M. OA-41-751-24  
 Eisenhut M.E. EP12-213-22  
 Ekanim I. EP11-199-22,  
 EP30-385-24,  
**EP32-404-24**  
 Ekeke N. OA-23-642-23,  
 EP07-166-21,  
 EP12-209-22,  
 EP14-233-22,  
 EP37-461-24  
 Ekka S. EP37-455-24  
 Ekqvist D. **OA-17-607-22**  
 Eldholm V. OA-35-714-24  
 Eldirdiri S. TBS-OA-14,  
 EP34-432-24  
 Elias Ntinginya N.  
 OA-18-617-22  
 Elizaga P. OA-36-725-24,  
 EP26-353-23  
 Ellis A. TBS-OA-02  
 Elmira E. OA-36-725-24,  
 EP26-353-23  
 Eloko G. OA-29-681-23  
 Elom E. EP19-280-22,  
 EP19-281-22,  
 EP36-447-24  
 El-Sadr W. EP22-308-23  
 Elsayed H. **OA-18-615-22**  
 Elskamp M. EP02-116-21  
 El Sony A. EP24-328-23  
 El-Tayeb O. EP16-256-22  
 Eman K.u. **EP21-298-23**  
 Emeka E. OA-03-516-21  
 Emery J. **OA-14-585-22**  
 Emery J.C. OA-31-688-23,  
**TBS-OA-07**  
 Emodi N. OA-23-644-23,  
 EP04-135-21, EP13-222-22  
 Eneogu R. EP08-172-21,  
 EP10-192-21,  
 EP19-286-22,  
 EP30-384-24,  
 EP31-394-24,  
 EP32-406-24,  
 EP32-409-24,  
 EP37-456-24  
 Eng S. OA-12-570-22,  
 EP13-227-22  
 Engelthaler D.  
 OA-35-717-24  
 England K. OA-29-686-23  
 Enock O. EP24-333-23  
 Epperson E. TBS-OA-12  
 Eremeeva N. EP-TBS-04  
 Ergeshov A. OA-11-567-22  
 Erkens C. OA-27-671-23  
 Ernest J. EP-TBS-67,  
**EP-TBS-81**, **EP-TBS-82**  
 Ershova J. OA-29-683-23,  
 EP28-367-23  
 Escudero J.N. EP-TBS-22  
 Eskinder B. **OA-36-722-24**  
 Esmail A. OA-17-610-22  
 Esmail H. OA-31-688-23,  
 EP03-119-21  
 Essalah L. EP36-450-24  
 Eudu J. OA-06-537-21  
 Evans D. EP16-253-22,  
 EP16-258-22,  
 EP22-315-23,  
 EP28-368-23  
 Everitt D. OA-17-610-22  
 Eze C. OA-23-642-23,  
 EP09-179-21,  
 EP12-209-22,  
 EP14-233-22  
 Eze C.C. EP07-166-21,  
 EP37-461-24  
 Ezeakile O. OA-23-642-23,  
 EP07-166-21,  
**EP12-209-22**,  
 EP14-233-22,  
 EP37-461-24  
 Ezeobi C. OA-14-589-22,  
 EP04-135-21  
 Ezeobi - Okoye C.  
**EP24-325-23**,  
**EP31-402-24**  
 Ezulu C. EP12-218-22
- F**  
 Fabella R.A. EP26-351-23  
 Faccin M. **OA-23-645-23**  
 Fadare O.A. EP12-216-22  
 Fadeyi M.O. **EP16-256-22**  
 Faguer B. OA-24-654-23  
 Fairhead C. **EP01-104-21**  
 Fairlie L. OA-02-513-21  
 Faisel A.J. EP06-157-21  
 Fajans M. OA-32-698-24,  
**EP11-206-22**  
 Fajardo E. OA-29-686-23  
 Falcão de Souza F.  
 OA-29-685-23  
 Fall A. EP07-165-21,  
 EP15-246-22  
 Falokun V. OA-14-588-22,  
 EP06-156-21,  
 EP09-179-21,  
 EP11-199-22,  
 EP19-286-22,  
 EP30-385-24,  
 EP32-404-24,  
 EP32-407-24  
 Falzon D. EP18-271-22  
 Fancourt N.S. EP07-162-21  
 Fandie R. **EP33-420-24**  
 Fang L. EP10-195-21  
 Faraj A. **EP27-354-23**  
 Farhat M. TBS-OA-12,  
 EP-TBS-56, EP-TBS-57  
 Farley J. OA-37-732-24  
 Farr K. EP15-248-22  
 Fätkenheuer G. EP-TBS-07  
 Faust L. OA-28-673-23  
 Faye S. OA-10-560-22,  
**OA-36-724-24**  
 Feasey H. EP-TBS-40  
 Febriani E. **EP20-292-23**  
 Feng C.-F. EP06-154-21,  
 EP22-309-23  
 Feng C.F. EP10-188-21  
 Ferdous F. EP11-202-22  
 Ferlazzo G. EP01-105-21  
 Fernandez L. EP12-213-22  
 Fernández L. OA-41-751-24  
 Fernández E. EP35-439-24  
 Fernández-Sanmartín M.A.  
 EP-TBS-03  
 Ferreira O. LB-2100-22  
 Ferro B.E. OA-28-679-23  
 Fetenesa B.A. **EP30-389-24**  
 Feuerriegel S. EP-TBS-53  
 Fielding K. **OA-34-712-24**,  
 LB-2046-24, LB-2087-24,  
 LB-2112-24,  
 EP13-219-22,  
 EP15-248-22  
 Figueroa J. OA-01-501-21  
 Figueroa J.E. OA-28-679-23  
 Finch S. EP26-346-23  
 Fine P. OA-34-712-24  
 Fischer P. LB-2100-22  
 Fischer J. EP-TBS-07  
 Fisher D. EP02-113-21  
 Fitzgibbon M. EP36-451-24  
 Flasche S. OA-14-585-22  
 Flook M. LB-2046-24  
 Florentino J. EP05-150-21  
 Florido M. EP-TBS-29  
 Floyd S. EP20-290-23,  
 EP24-332-23  
 Fonseca Rosário N.  
 EP-TBS-19  
 Font H. EP12-215-22

- Foray L. EP-TBS-53  
 Ford N. OA-01-503-21  
 Forse R.J. OA-07-547-21,  
 OA-28-674-23,  
 EP10-194-21  
 Forse R. EP16-257-22,  
 EP31-396-24  
 Fouad Kamara R. EP-TBS-53  
 Fox G. OA-12-576-22,  
 OA-36-723-24,  
 EP25-341-23  
 Fox G.J. OA-19-624-22,  
 OA-36-726-24,  
 EP31-399-24  
 Fox J. G. EP22-314-23  
 Francis D. LB-2047-21  
 Francis Munjattu J.  
 EP33-416-24  
 Franke M. EP-TBS-80  
 Frascella B. **OA-31-688-23**  
 Fregonese F. OA-07-542-21,  
 EP02-113-21  
 Freitas Lopez D.B.  
 EP01-106-21  
 French N. LB-2112-24  
 Freschi L. EP-TBS-56,  
**EP-TBS-57**  
 Frick M. EP02-115-21,  
 EP02-116-21  
 Friedland G. OA-06-540-21,  
 OA-12-573-22  
 Friedland J.S. OA-27-668-23  
 Frimpong-Mansoh R.  
 OA-07-546-21  
 Fu L. **OA-05-535-21,**  
**EP09-182-21, EP-TBS-58**  
 Fu M. EP35-439-24  
 Fukutani K.F. EP-TBS-15  
 Fulas D. EP30-389-24  
 Fulcher I. EP-TBS-80  
 Funk S. OA-14-585-22  
 Furin J. LB-2090-22,  
 EP07-167-21,  
 EP17-265-22,  
 EP17-266-22  
 Furió V. LB-2082-21,  
**EP-TBS-51**  
 Fynn E. EP19-284-22
- G**  
 Gabillard D. OA-01-503-21  
 Gaborets T. OA-04-527-21  
 Gabrielian A.  
 OA-05-534-21,  
 OA-19-625-22,  
 OA-35-718-24,  
 EP-TBS-49, EP-TBS-55  
 Gadanya M. EP06-156-21  
 Gagneux S. OA-13-581-22,  
 OA-27-672-23,  
 OA-35-716-24,  
 EP-TBS-49  
 Gajere J.B. OA-23-640-23,  
 EP14-235-22  
 Galea J. EP04-134-21,  
 EP09-180-21,  
 EP12-211-22  
 Galea J.T. EP34-426-24
- Galiwango R.  
 OA-15-597-22  
 Gama H. **OA-21-631-22**  
 Gamazina K. OA-04-523-21,  
 OA-04-526-21,  
 OA-04-527-21  
 Gande S. EP10-187-21,  
 EP30-385-24,  
 EP31-394-24,  
 EP32-407-24  
 Gandhi R. OA-26-662-23,  
 EP03-118-21  
 Ganiem A.R. TBS-OA-01  
 Gao L. LB-2070-24  
 Gao J. EP09-183-21  
 Garba Ado A.  
 OA-03-516-21  
 Garcia Baena I.  
**OA-29-681-23,**  
**EP28-364-23,**  
 EP28-365-23  
 Garcia-Basteiro A.  
 EP12-212-22  
 García-García E.  
 EP27-355-23  
 García Marin A.M.  
**LB-2082-21**  
 Garcia-Prats A.J.  
 OA-17-611-22  
 Gardner A. EP11-203-22  
 Garfin A.M.C.  
 OA-13-580-22,  
 EP19-278-22,  
 EP26-351-23,  
 EP28-364-23  
 Garfin C. OA-35-717-24,  
 EP01-103-21,  
 EP05-150-21,  
 EP13-221-22  
 Garfin A. EP30-393-24  
 Garfin A.M.C.G.  
 EP33-414-24  
 Garg T. EP15-247-22,  
 EP26-350-23,  
 EP37-462-24  
 Gashaw M. OA-38-740-24  
 Gatechompol S.  
**EP11-201-22**  
 Gautier J. OA-05-532-21  
 Gaviola D.M. EP05-150-21,  
 EP19-278-22,  
 EP26-351-23  
 Gavu-Tshawe Z.  
 OA-22-639-23  
 Gcwensa N. EP20-294-23  
 Geldmacher C. EP-TBS-11,  
 EP-TBS-12  
 Genade L. OA-23-646-23  
 Geocaniga-Gaviola D.M.  
 OA-13-580-22,  
 EP28-364-23  
 George G. EP22-308-23  
 Georghiou S.  
 OA-38-737-24,  
 OA-38-741-24  
 Gerasimova A. EP29-379-24  
 Gerbl F. EP36-453-24  
 Geric\* C. LB-2047-21  
 Gessner S. TBS-OA-08
- Ggita J.M. OA-12-572-22  
 Ggita J. OA-18-613-22  
 Ghafoor A. **EP09-178-21**  
 Ghariani A. EP36-450-24  
 Ghim J.-L. EP-TBS-77,  
 EP-TBS-78, EP-TBS-79  
 Ghimire S. **EP27-363-23**  
 Ghita E. OA-35-718-24  
 Ghosh S. OA-36-722-24,  
**EP26-344-23,**  
**EP26-347-23**  
 Ghule V. **EP37-455-24,**  
 EP37-464-24  
 Giacomet C. EP19-282-22  
 Gibb D.M. OA-02-513-21,  
 LB-2056-24, EP02-114-21  
 Gidado M. OA-16-603-22,  
**EP06-152-21,**  
 EP09-179-21,  
 EP10-187-21,  
 EP19-280-22,  
 EP19-281-22,  
 EP32-406-24,  
**EP32-411-24,**  
 EP36-447-24  
 Giglio P. OA-05-529-21  
 Giguashvili A. **EP29-378-24**  
 Gillespie S.H.  
 OA-03-517-21,  
 OA-25-659-23,  
 OA-35-713-24,  
 TBS-OA-14, EP34-429-24,  
 EP34-432-24,  
 EP34-435-24  
 Gillespie S. OA-18-617-22,  
 OA-24-648-23,  
 EP02-117-21  
 Gilman R. OA-05-533-21  
 Girma B. EP14-230-22,  
 EP14-231-22,  
 EP14-236-22,  
 EP14-238-22,  
 EP21-301-23  
 Girma M. EP16-258-22  
 Githiomi M. EP-TBS-66  
 Gituku C. **EP11-203-22**  
 Gleim J. TBS-OA-02  
 Glynn J. OA-34-712-24  
 Gnagnou S. EP23-319-23,  
 EP23-322-23  
 Gnakadja N. EP19-283-22  
 Gning B. EP07-165-21  
 Godebo M. EP18-276-22  
 Gody J.-C. EP23-319-23  
 Gody J. EP23-322-23  
 Goel N. EP32-413-24  
 Goldman R. OA-02-511-21  
 Goldmann T. TBS-OA-04  
 Goletti D. OA-27-668-23  
 Golub J. OA-01-503-21,  
 OA-15-594-22  
 Golubkov A. EP01-103-21  
 Gomathi N. OA-34-711-24,  
 EP01-100-21  
 Gomathi S. OA-38-735-24  
 Gombe M. OA-07-546-21  
 Gomes I. **EP06-157-21,**  
 EP16-251-22  
 Gomes N. **EP12-212-22**
- Gomes dos Santos A.P.  
 EP-TBS-16, EP-TBS-24  
 Gomez G.B. EP28-374-23,  
 EP-TBS-34  
 Gomez Paciello L.  
 EP27-363-23  
 Gones V. **OA-36-725-24,**  
**EP26-353-23**  
 Gonzales C. OA-41-752-24  
 Goodall R. OA-17-606-22  
 Goosby E. OA-29-680-23  
 Gorbach L. **EP-TBS-32**  
 Goswami A. OA-21-629-22,  
 EP14-237-22, EP33-417-24  
 Goswami N.D.  
 OA-26-665-23,  
 OA-26-666-23,  
 EP26-352-23  
 Gotuzzo E. EP-TBS-38  
 Gouda S. EP09-186-21  
 Goupeyou A.W.  
 EP23-322-23  
 Govathson C. EP16-253-22,  
 EP28-368-23  
 Govender I. EP01-104-21,  
**EP32-410-24**  
 Gozalov O. OA-04-528-21  
 Gqada M. TBS-OA-08  
 Graciaa D.S. **TBS-OA-09**  
 Graham S.M. EP02-112-21,  
 EP24-331-23  
 Graham C. EP26-346-23  
 Grammatico M. LB-2127-24  
 Grandjean L. OA-35-714-24  
 Grankov V. OA-04-525-21,  
 OA-04-528-21,  
 EP01-107-21,  
 EP29-383-24  
 Grant A. OA-09-554-21,  
 OA-17-609-22,  
 OA-35-714-24,  
 EP01-104-21,  
 EP01-109-21,  
 EP05-148-21,  
 EP32-410-24  
 Gray A. EP03-119-21  
 Green A. **EP-TBS-56**  
 Greenaway C.  
 OA-27-668-23  
 Greenfield S. LB-2119-21  
 Greg F. EP10-190-21  
 Grobbel H.-P. **EP-TBS-50**  
 Gu J. OA-19-625-22  
 Gubernat A. TBS-OA-02  
 Guidotti G. OA-05-529-21  
 Guirgis S. EP26-351-23,  
 EP30-393-24  
 Gujabidze M.  
 OA-40-742-24  
 Gumbo T. EP09-176-21  
 Gumenuik M.  
 OA-19-622-22  
 Gumma V. OA-16-600-22  
 GUMMA V. OA-16-598-22  
 Gumusboga M.  
 EP19-283-22  
 Gunasekera K.  
**OA-11-566-22**  
 Gunda A. OA-10-558-22

- Gunda R. EP32-410-24  
 Günther G. TBS-OA-04  
 Guo X. OA-32-694-24  
 Gupta S. OA-26-662-23  
 Gupta R. OA-28-673-23  
 Gupta A. EP09-184-21,  
 EP27-357-23,  
 EP30-386-24, EP-TBS-10,  
 EP-TBS-15, EP-TBS-41  
 Gupta P. **EP-TBS-28**  
 Gupta R.K. EP-TBS-42  
 Gupta T. **EP-TBS-62**  
 Gupte N. EP12-208-22,  
 EP30-386-24  
 Gurbanova E.  
 OA-04-528-21,  
 EP01-107-21  
 Gurumurthy M.  
**EP02-111-21**  
 Gwanzura C. OA-09-552-21
- H**  
 Haas W. OA-27-670-23,  
 EP29-376-24  
 Habib S. EP37-463-24  
 Hahn L. OA-37-732-24  
 Hailemeskel F.  
 OA-36-722-24  
 Haldane V. **EP05-149-21**  
 Haldar S. EP-TBS-42  
 Hallett T. EP28-372-23  
 Hamada Y. OA-28-673-23  
 Hamaguchi Y. EP33-424-24  
 Hambwalula R.  
 OA-07-544-21,  
 EP18-270-22  
 Hammond R. **EP02-117-21**  
 Hammoudi F. EP23-322-23  
 Hananiya D.S.  
**OA-23-640-23,**  
**EP14-235-22**  
 Hananiya D. EP20-289-23  
 Hang N.T.L. EP-TBS-08  
 Hanif M. OA-19-619-22  
 Hanrahan C. OA-02-509-21,  
 OA-28-676-23,  
 OA-28-677-23  
 Hanson-Nortey N.N.  
 EP05-142-21  
 Hansoti B. OA-37-732-24  
 Haque R. EP08-168-21,  
 EP33-422-24, EP37-457-24  
 Harding J. EP09-176-21  
 Hargreaves S.  
 OA-27-668-23  
 Harris R.C. **OA-14-587-22,**  
 EP06-155-21  
 Harris R. OA-27-667-23,  
 EP28-374-23, EP-TBS-34  
 Harris M. OA-35-718-24,  
**EP-TBS-55**  
 Harrison T. EP02-110-21  
 Harrison M. EP26-349-23  
 Haselau P. EP13-228-22  
 Hashiguchi L. OA-24-654-23  
 Hassan M. **EP24-328-23**  
 Hassane Harouna S.  
**EP13-220-22**
- Hatherill M. TBS-OA-06  
 Hauer B. EP29-376-24  
 He X. OA-09-555-21,  
**EP13-229-22,**  
 EP22-317-23,  
 EP34-427-24  
 He J. LB-2070-24  
 He M. EP09-183-21  
 Hedges K. **EP02-115-21,**  
 EP02-116-21  
 Heekes A. EP04-129-21  
 Hegde A. OA-26-662-23,  
 EP03-118-21  
 Heinrich N. OA-35-713-24  
 Helfinstein S. OA-22-634-23  
 Hellewell J. OA-14-585-22  
 Hemanth Kumar A.K.  
**EP01-100-21**  
 Hendricks P. EP03-125-21  
 Heneine E. **OA-03-521-21**  
 Hesseling A.C.  
 OA-02-513-21,  
 OA-11-566-22,  
 OA-17-611-22,  
 OA-21-632-22,  
 OA-28-675-23,  
 LB-2056-24, EP02-112-21,  
 EP04-131-21,  
 EP23-324-23  
 Hesseling A. EP04-129-21  
 Hessling A.C. EP02-114-21  
 Hewison C. EP-TBS-80  
 Heyckendorf J. **TBS-OA-04,**  
 EP-TBS-06, EP-TBS-50,  
 EP-TBS-53  
 Heysell S. OA-37-729-24,  
 LB-2119-21, EP11-197-22,  
 EP-TBS-72, EP-TBS-76  
 Heysell S.K. EP34-435-24  
 Hierce M. EP36-454-24  
 Higdon M. EP07-162-21  
 Hijikata M. EP-TBS-08  
 Hill J. OA-09-554-21,  
 EP05-148-21  
 Hill A. EP-TBS-61  
 Hillemann D. EP-TBS-50  
 Hirasen K. **EP16-253-22,**  
**EP28-368-23**  
 Hirsch-Moverman Y.  
**EP22-308-23**  
 Hissar S. **OA-34-711-24,**  
 LB-2056-24, EP02-114-21  
 HL M. OA-06-536-21,  
 EP33-415-24, EP33-416-24  
 Hmun T. **EP09-185-21**  
 Ho J. OA-19-624-22  
 Ho C. EP21-302-23  
 Hoang T.H. OA-36-726-24,  
 EP31-399-24  
 Hoang N.P. EP-TBS-08  
 Hochberg N. EP28-370-23  
 Hoddinott G. EP03-125-21,  
 EP15-241-22  
 Hodges J. **EP11-197-22**  
 Hoelscher M. TBS-OA-04  
 Hoelscher M. OA-35-713-24  
 Hoffmann H.  
 OA-38-741-24,  
 EP36-453-24, EP-TBS-50
- Hoffner S. EP-TBS-59  
 Hofmann-Thiel S.  
 EP36-453-24  
 Holmgren C. EP01-105-21,  
 EP33-418-24  
 Holtzman D. EP11-207-22  
 Hoque S. EP15-244-22  
 Horn C. EP-TBS-07  
 Horne R. OA-04-522-21  
 Horne D.J. OA-05-531-21  
 Horne D. EP24-331-23  
 Horsburgh R. OA-25-658-23  
 Horsburgh C.R.  
 OA-32-697-24,  
 EP09-177-21, EP22-318-23  
 Horsburgh, Jr. C.  
 EP28-370-23  
 Hossain F. OA-41-748-24,  
 EP33-418-24  
 Hota P.K. OA-21-626-22,  
 EP09-186-21, EP15-239-22  
 Hou S. EP22-316-23  
 Hou X. EP-TBS-22  
 Houben R. OA-14-585-22,  
 EP28-373-23  
 Houben R.M. OA-14-587-22  
 Houben R.M.G.J.  
 OA-31-688-23, TBS-OA-07  
 Hout E. OA-37-729-24,  
 LB-2119-21  
 Howard A. OA-09-552-21  
 Howard A.A. EP22-308-23  
 Howard R. **EP-TBS-52**  
 Howell P. OA-17-610-22  
 Hsu L.Y. OA-12-570-22,  
 OA-18-614-22,  
 EP13-227-22  
 Htwe M.M. OA-35-720-24  
 Hu J. OA-26-664-23,  
 EP05-149-21  
 Hu Y. EP34-430-24,  
 EP-TBS-59  
 Hu C. EP-TBS-18  
 Hu T. **EP-TBS-45**  
 Huan H.V. EP-TBS-08  
 Huang H.-L. OA-07-545-21,  
**OA-07-548-21**  
 Huang C.-C. OA-33-703-24  
 Huang M. **EP04-132-21,**  
**EP36-448-24**  
 Huang Y.-F. EP06-154-21,  
 EP22-309-23  
 Huang Y.-C. EP06-154-21,  
 EP22-309-23  
 Huang Y.F. EP10-188-21  
 Huang C.C. EP23-320-23,  
 EP-TBS-02  
 Huang E.W.-C. **EP25-341-23**  
 Huang K. EP26-346-23  
 Huaroto L. OA-05-533-21  
 Huerga H. EP-TBS-80  
 Hughes G. **OA-17-608-22**  
 Hughes J. EP01-102-21,  
 EP03-119-21,  
 EP04-131-21,  
 EP07-167-21,  
 EP12-218-22  
 Hui Teng L. EP-TBS-20  
 Huang N.T. EP-TBS-64
- Huque R. EP35-436-24  
 Hurevich H. OA-04-525-21,  
 OA-04-528-21,  
 EP01-107-21, EP29-383-24  
 Hurisa M.B. EP30-389-24  
 Hurt D. OA-05-534-21,  
 OA-19-625-22,  
 OA-35-718-24, EP-TBS-55  
 Hussain H. OA-34-710-24,  
 OA-41-748-24,  
 EP06-157-21,  
 EP37-463-24  
 Hussein H. EP24-328-23  
 Hussien R. EP24-328-23  
 Hutchinson B.  
**OA-33-706-24**  
 Huynh H. EP16-257-22,  
 EP31-396-24
- I**  
 Ibanda I. OA-25-660-23  
 Ibeziako V. OA-14-589-22,  
 EP04-135-21,  
 EP13-222-22,  
 EP20-289-23,  
 EP30-392-24  
 Ibna Mohsin S.M.  
**EP15-244-22,**  
 EP17-264-22,  
**EP33-422-24**  
 Ibne Mohsin S.M.  
 EP08-168-21  
 Ibraim E. TBS-OA-04  
 Igboekwu C. EP30-392-24  
 Igunza P. OA-10-559-22  
 Ihesie C.A. **EP11-199-22**  
 Ihesie A. EP32-404-24  
 Ijaz A. OA-41-753-24  
 Ikebudu J. OA-23-642-23,  
 EP12-209-22  
 Ikebudu J.N. EP37-461-24  
 Ikeda S. **OA-31-692-23**  
 Ikram A.N. EP21-306-23  
 Ikua W. OA-21-630-22  
 iliya S. EP34-433-24  
 Illozumba J. EP24-325-23,  
 EP31-402-24  
 Illozumba J. OA-14-589-22  
 Ilunga V. **OA-15-596-22**  
 Ilyasova E. OA-04-525-21  
 Imoniero G. EP12-216-22  
 Imperial M. TBS-OA-15,  
 EP-TBS-65, **EP-TBS-69,**  
**EP-TBS-73,** EP-TBS-84  
 In H.K. OA-32-699-24  
 In H. EP04-128-21  
 Inoue Y. EP-TBS-60  
 Iribarren S. **EP05-145-21,**  
 EP22-311-23  
 Iroko A. **OA-19-623-22,**  
 EP16-261-22,  
**EP17-268-22,** EP37-456-24  
 Isaakidis P. OA-24-653-23,  
 LB-2090-22, EP01-105-21,  
 EP17-265-22,  
 EP17-266-22,  
 EP29-380-24,  
 EP33-418-24

- Ishengoma L. EP20-293-23  
 Isidoro-Gonçalves L.  
 OA-29-685-23,  
 EP16-259-22  
 Islam M.S. OA-41-748-24  
 Islam S. EP06-157-21,  
 EP26-346-23  
 Islam A. EP15-244-22  
 Islam M.A. EP17-264-22,  
 EP33-422-24, EP37-457-24  
 Islam T. EP28-367-23  
 Ismael N. EP21-305-23  
 Ismagilova T. **OA-14-591-22**,  
 OA-21-628-22  
 Ismail F. EP21-305-23  
 Ismayilov A. OA-10-562-22,  
 OA-15-593-22,  
 EP05-147-21, EP12-217-22  
 Isooba D. OA-24-652-23  
 Isralls S. **OA-17-609-22**  
 Ito E. EP-TBS-36  
 Ivanova O. OA-03-519-21,  
 OA-40-743-24,  
 EP22-315-23,  
 EP25-342-23,  
 EP28-368-23  
 Ivanova Reipold E.  
 EP-TBS-38  
 Iyer A. EP01-105-21  
 Izquierdo-Garcia J.L.  
 OA-05-532-21,  
 EP27-355-23  
 Izumi K. EP28-366-23
- J**  
 Jackson J. EP-TBS-33  
 Jackson-Sillah D. EP-TBS-23,  
 EP-TBS-44  
 Jacobson K.R.  
 OA-32-697-24,  
 EP09-177-21,  
 EP22-318-23  
 Jacobson K. EP01-102-21  
 Jadambaa N. EP28-367-23  
 Jagadeesan M  
 OA-22-634-23  
 Jaganath D. OA-11-565-22,  
**OA-38-736-24**,  
 OA-38-738-24  
 Jagaty S.K. **EP-TBS-70**  
 Jagwer G. EP16-255-22,  
 EP21-300-23  
 Jain A. EP37-459-24  
 Jaiswal P. EP26-353-23  
 Jajou R. OA-32-695-24  
 Jaju J. OA-26-663-23,  
**EP05-141-21**  
 Jaju A. EP-TBS-74  
 Jamal W. **EP37-463-24**  
 James Kitonsa P.  
 OA-24-652-23  
 Jamison D. OA-29-680-23  
 Jan S. OA-36-726-24,  
 OA-36-726-24,  
 EP31-399-24  
 Jani B. OA-29-683-23  
 Janmohamed A.  
 OA-41-753-24
- Jansen K. OA-27-669-23  
 Jansen N. EP10-193-21,  
 EP29-381-24  
 Jantjies M. OA-22-635-23  
 Jaoko W. EP24-331-23  
 Jarlsberg L. EP-TBS-65,  
**EP-TBS-84**  
 Jarrett B. OA-15-594-22  
 Jassat W. **OA-13-578-22**  
 Jaswal M. OA-34-710-24,  
 EP37-463-24  
 Javaid L. EP15-245-22  
 Jayabal L. EP-TBS-47  
 Jayaram M. **EP-TBS-20**  
 Jean Couste M.D.  
 OA-05-532-21  
 Jeffrey B. **OA-35-718-24**,  
 EP-TBS-55  
 Jele V. EP33-419-24  
 Jenkins H. **EP01-102-21**,  
**EP04-134-21**,  
 EP14-234-22,  
 EP23-321-23  
 Jens L. EP06-152-21,  
 EP32-411-24  
 Jensen C. OA-03-521-21  
 Jenum S. LB-2092-21  
 Jeon H. EP-TBS-27  
 Jeong H. EP-TBS-17  
 Jerene D. OA-09-550-21,  
 EP18-276-22, EP37-460-24  
 Jiang W. OA-29-684-23  
 Jichkar S. OA-26-662-23  
 Jimenez J. EP04-134-21,  
 EP09-180-21, EP14-234-22  
 Jiménez-Garcia J.  
**OA-28-679-23**  
 Jimenez Guevara J.  
 EP34-426-24  
 Jin Q. LB-2070-24  
 Jindani A. EP02-110-21  
 Jivan D. OA-21-632-22  
 Jo Y. EP06-157-21  
 Joekes E. EP25-335-23  
 John J. OA-18-617-22  
 Johns B. OA-10-560-22,  
 OA-36-724-24  
 John\_Stewart G.  
 OA-01-506-21  
 John-Stewart G.  
 OA-01-501-21, EP-TBS-22  
 Johnston J.C. OA-07-542-21  
 Johnston J. OA-19-624-22,  
 EP02-113-21  
 Jolayemi T. EP32-408-24  
 Joloba M. OA-15-597-22,  
 OA-25-660-23,  
 OA-37-731-24,  
 LB-2087-24, EP16-252-22,  
 EP18-274-22, EP36-452-24  
 Jondhale V. OA-26-662-23,  
 EP03-118-21  
 Jones A.S.K. OA-04-522-21  
 Jones J. LB-2127-24  
 Jones H. EP25-336-23  
 Jongedijk E. EP-TBS-76  
 Jonsson Nordvall M.  
 OA-17-607-22  
 Jose M.B. EP12-216-22
- Joseph R. OA-10-558-22  
 Joseph B. OA-34-711-24,  
 EP15-241-22,  
 EP19-281-22,  
 EP34-433-24  
 Joshi C. OA-09-553-21  
 Joshi S. EP12-208-22  
 Joshi B. **EP12-215-22**  
 Joshi D. EP34-428-24  
 Jou R. OA-25-656-23,  
 OA-35-715-24,  
 EP06-154-21  
 Jouego C.G. **OA-13-579-22**  
 Jouet A. EP-TBS-53  
 J. Svensson R. EP27-354-23  
 Jugheli L. OA-27-672-23  
 Jung N. EP-TBS-07  
 Jung J. **EP-TBS-17**  
 Justine M. OA-37-729-24,  
 LB-2119-21
- K**  
 K R. OA-19-619-22  
 K K. EP33-415-24  
 Kabaso M. EP06-158-21  
 Kabia E. EP16-254-22  
 Kabuayi J.-P. OA-23-645-23  
 Kabugo J. OA-25-660-23,  
 EP36-452-24  
 Kadota J. **EP13-226-22**  
 Kaggia S. EP06-153-21  
 Kagujje M. OA-07-544-21,  
 EP18-270-22, EP36-454-24  
 Kagwiria D. OA-19-620-22  
 Kaipilyawar S. **EP21-302-23**  
 Kaira D. EP03-126-21  
 Kairu A. **EP16-254-22**  
 Kaiser N. EP-TBS-77  
 Kakaire R. OA-15-597-22,  
 OA-26-661-23  
 Kakayeva S. OA-02-512-21,  
**OA-23-643-23**,  
 OA-41-747-24,  
 EP07-159-21, **EP07-160-21**  
 Kakeeto A. EP34-431-24  
 Kakinda M. **OA-29-687-23**,  
**EP36-445-24**  
 Kal M. **EP28-367-23**  
 Kalottee B. **EP37-459-24**  
 Kalra A. EP37-455-24,  
**EP37-464-24**  
 Kalsdorf B. TBS-OA-04,  
 EP-TBS-50  
 Kamau S. EP26-345-23  
 Kambili C. EP28-371-23  
 Kambinda P. EP19-284-22  
 Kamiya Y. OA-37-728-24  
 Kamoga C. OA-31-689-23  
 Kamwela M. EP21-301-23  
 Kamweru L. EP26-345-23  
 Kamyia M. EP36-449-24  
 Kanchar A. EP18-271-22  
 Kandeepan S. EP35-441-24,  
 EP35-442-24,  
 EP35-443-24,  
 EP35-444-24  
 Kandulu C. LB-2112-24  
 Kane M. EP07-165-21
- Kang J. OA-32-694-24  
 Kang K. EP22-313-23  
 Kang Y.A. EP-TBS-27  
 Kangave F. OA-25-660-23  
 Kangongwe M.  
 OA-25-657-23  
 Kannan T. EP01-100-21  
 Kanyerere H. **EP14-230-22**,  
 EP14-238-22,  
 EP15-240-22,  
 EP15-242-22,  
**EP15-243-22**,  
**EP21-301-23**  
 Kaos Majwala R.  
 OA-37-731-24,  
 EP36-452-24  
 Kapadiya D. OA-09-553-21  
 Kapasa M. EP23-323-23  
 Kapoor S. EP35-439-24  
 Kar A. EP33-415-24  
 Karakousis P.C. EP-TBS-15  
 Karanda V. OA-14-591-22  
 Karat A.S. **OA-04-522-21**  
 Karat A. EP01-104-21,  
 EP32-410-24  
 Karea I. OA-05-529-21  
 Karim F. OA-24-647-23,  
 EP-TBS-01  
 Karoney M. EP11-203-22  
 Karskanova S. EP-TBS-14  
 Kasaeva T. EP18-271-22  
 Kasapo C. EP06-158-21  
 Kasapo C.C. **EP21-303-23**  
 Kashongwe Z. EP-TBS-54  
 Kasibante J. LB-1968-21  
 Kassim S. OA-10-559-22  
 Kaswa M. OA-23-645-23,  
 OA-29-681-23, EP-TBS-54  
 Kaswaswa K. **EP14-236-22**,  
 EP14-238-22  
 Katamba A. OA-02-509-21,  
 OA-12-572-22,  
 OA-18-613-22,  
 OA-24-652-23,  
 OA-31-689-23,  
 LB-2087-24, EP13-219-22,  
 EP13-224-22,  
 EP13-226-22,  
 EP15-248-22  
 Katana A. OA-01-504-21  
 Katende J. EP36-449-24  
 Katete A. EP03-126-21  
 Kato-Maeda M.  
 OA-13-580-22,  
 OA-31-689-23,  
 OA-35-717-24  
 Katota P. OA-16-604-22  
 Katuramu R. OA-13-582-22,  
 OA-13-583-22,  
 OA-13-584-22  
 Kau M. EP33-414-24  
 Kaufmann S.H. TBS-OA-04  
 Kawatsu L. OA-14-586-22,  
**EP33-424-24**  
 Kawen M. OA-37-730-24  
 Kawuma J. EP18-269-22  
 Kay A. OA-21-631-22,  
**OA-41-751-24**,  
**EP12-213-22**



- Kay A.W. OA-28-675-23  
 Kayembe B. OA-32-698-24  
 Kazakov A. EP-TBS-63  
 Kazi G.N. EP21-298-23  
 Kazibwe A. OA-12-571-22,  
 OA-22-637-23  
 Kazounis E. **OA-32-700-24**  
 Kazwala R. EP-TBS-44  
 K.B Matovu J.  
 OA-29-687-23,  
 EP36-445-24  
 Keam T. EP26-346-23  
 Kebede W. OA-38-740-24  
 Kee S.-J. EP-TBS-17  
 Keene C. EP17-265-22,  
 EP17-266-22  
 Keicho N. **EP-TBS-08**  
 Kekitiinwa A.R.  
 EP18-275-22  
 Kelamane S. EP31-395-24,  
 EP31-401-24  
 Kelly M.S. OA-03-515-21,  
 EP25-337-23  
 Kelly-Cirino C. LB-2100-22  
 Kemp H. OA-22-634-23  
 Kempker R. OA-27-672-23,  
 OA-40-742-24,  
 TBS-OA-09, EP29-378-24,  
 EP-TBS-49  
 Kendall E. OA-02-509-21,  
**OA-31-689-23**  
 Kendall-Carpenter E.  
 EP26-346-23  
 Kenyi Lodiongo D.  
**EP18-277-22**  
 Keo S. OA-23-641-23  
 Kerkhoff A. LB-1903-23  
 Kerr S.J. EP11-201-22  
 Kerubo L. EP-TBS-66  
 Keshavjee S. EP04-134-21,  
 EP09-180-21,  
 EP14-234-22  
 Keshavjee S.A. EP34-426-24  
 Khan A. OA-10-556-22,  
 OA-26-662-23,  
 EP03-118-21,  
 EP16-251-22,  
 EP34-428-24  
 Khan K. OA-24-647-23,  
 EP-TBS-01  
 Khan S. OA-34-710-24  
 Khan A.J. OA-37-734-24  
 Khan U. OA-41-753-24,  
 EP-TBS-80  
 Khan P. OA-41-753-24,  
 EP-TBS-80  
 Khan M. LB-2071-23  
 Khaniukov I. OA-04-527-21  
 Khanna A. OA-19-619-22,  
 OA-33-704-24,  
 EP31-398-24  
 Khanna A.K. EP26-347-23  
 Khan Niazi S.U.  
 EP08-171-21  
 Khaparde K. EP15-249-22  
 Khara B. OA-21-626-22  
 Kharat A. **LB-2113-22**,  
**EP-TBS-74**  
 Khatri U. EP13-221-22  
 Khine M.K. **EP19-279-22**  
 Khosa C. OA-40-743-24,  
 EP12-215-22,  
 EP22-315-23,  
 EP28-368-23  
 Khundi M. EP-TBS-40  
 Khunga M. EP21-303-23  
 Khurtsilava I. EP-TBS-49  
 Kibiki G.S. OA-25-659-23,  
 OA-35-713-24,  
 EP34-432-24  
 Kibiki G. TBS-OA-14  
 Kidd M. LB-2092-21  
 Kielmann K. OA-04-522-21,  
 OA-09-554-21,  
 EP01-109-21,  
 EP05-148-21  
 Kierre N. EP-TBS-54  
 Kilale A.M. **OA-29-683-23**  
 Killian J.A. **LB-2115-21**  
 Kiluba J.-C. OA-01-500-21,  
 OA-37-730-24  
 Kim J.M. OA-07-542-21  
 Kim H. **EP04-128-21**  
 Kim T.S. EP27-360-23  
 Kim C.-K. **EP27-360-23**  
 Kim S.-H. EP-TBS-17  
 Kim J. EP-TBS-27  
 Kim E.-Y. EP-TBS-78,  
 EP-TBS-79  
 Kim D.-H. EP-TBS-79  
 King C. OA-03-514-21,  
 EP25-339-23  
 Kinghorn A. OA-23-646-23  
 Kinikar A. OA-34-711-24,  
 EP12-208-22, EP-TBS-15  
 Kinikar A.A. EP02-114-21  
 Kinuthia J. OA-01-506-21  
 Kipiani M. OA-40-742-24,  
 TBS-OA-09  
 Kiptai T. OA-10-559-22  
 Kirabirwa N. OA-12-571-22  
 Kirathe D. EP25-335-23  
 Kirchner H.L. OA-28-675-23  
 Kirimunda S. **OA-15-597-22**  
 Kirirabwa N. OA-13-584-22  
 Kirking H.L. EP18-275-22  
 Kirubi B. **OA-29-682-23**  
 Kisamba H. **OA-18-618-22**  
 Kiseleva E. OA-11-567-22  
 KishoreReddy V.  
 OA-16-598-22  
 Kiskadden-Bechtel S.  
 OA-26-666-23,  
 EP26-352-23  
 Kisomb J. EP28-367-23  
 Kitonsa P. OA-02-509-21,  
 OA-31-689-23  
 Kityamuwesi A.  
**OA-18-613-22**  
 Kiwanuka N.  
 OA-15-597-22,  
 OA-26-661-23  
 Kiyemba T. **OA-12-571-22**,  
 OA-15-592-22,  
 EP30-390-24  
 Kizito E. OA-13-582-22,  
**OA-14-590-22**,  
**EP04-139-21**  
 Kizito H. OA-14-590-22,  
**OA-22-636-23**,  
 EP03-124-21,  
 EP34-431-24  
 Klaassen D. EP10-193-21  
 Klein K. EP22-311-23  
 Klevno N. EP-TBS-63  
 Klimenko N. OA-04-523-21  
 Klimuk D. OA-04-525-21,  
 OA-04-528-21,  
 EP01-107-21  
 Klinkenberg D.  
 OA-32-695-24  
 Klinkenberg E. EP20-290-23  
 Klopogge F. EP02-117-21  
 Klueppelberg R.  
**EP13-225-22**  
 Knight G. OA-14-585-22  
 Knoll M. EP07-162-21  
 Kodethoor D.  
 OA-19-619-22  
 Koedoot N. EP11-198-22  
 Koeken V.A. **TBS-OA-01**  
 Koeltringer F.A.  
**EP04-138-21**  
 Koh M. EP11-202-22  
 Kohl T. EP-TBS-50,  
 EP-TBS-53  
 Köhler N. EP-TBS-50  
 Kohli M. EP19-285-22  
 Komakech W. EP30-392-24  
 Komrska J. OA-17-606-22  
 Kong K. OA-23-641-23  
 Kontsevaja I. TBS-OA-04  
 Korobitsyn A.  
 OA-28-673-23  
 Korotych O. OA-21-628-22  
 Korthals Altes H.  
**OA-32-695-24**,  
 EP29-377-24  
 Kose J. EP11-204-22  
 Koshcheyev M.  
 EP11-197-22  
 Koshkina O. EP11-197-22  
 Kosloff B. **OA-38-739-24**,  
 EP20-290-23  
 Kostkova P. EP03-119-21  
 Koura K.G. **EP23-319-23**,  
**EP23-322-23**  
 Kourav J. OA-06-538-21  
 Kovtunovich L.  
 OA-04-526-21  
 Koyio L. OA-19-620-22,  
 OA-21-630-22  
 Krainski E.T. EP01-101-21  
 Kranzer K. EP28-373-23  
 Krause G. EP31-397-24  
 Kribbs J. EP20-296-23  
 Krieger M.A. EP-TBS-37  
 Kröger S. OA-27-670-23,  
 EP29-376-24  
 Kruger J. OA-32-698-24  
 Kruger L.J. LB-2093-22  
 Krutikov M. **OA-28-673-23**  
 Ku C.-C. **EP-TBS-40**  
 Kuate A. OA-13-579-22  
 Kucharski A. OA-14-585-22  
 Kuhlin J. EP34-430-24  
 Kuijpers S. EP29-381-24  
 Kula N. EP16-255-22  
 Kulkarni V. LB-2113-22,  
 EP27-357-23,  
 EP30-386-24, EP-TBS-10,  
 EP-TBS-41, EP-TBS-74  
 Kuma A. **EP26-346-23**  
 Kumar N. OA-16-598-22  
 Kumar N. OA-16-600-22,  
 EP15-247-22  
 Kumar S. OA-21-629-22,  
 EP14-237-22,  
 EP33-417-24  
 Kumar V. TBS-OA-01,  
 EP09-184-21  
 Kumar S. EP01-100-21  
 Kumar M. EP15-247-22  
 Kumar A. EP26-347-23,  
 EP26-351-23  
 Kumar P. EP27-357-23  
 Kumar Nathella P.  
 EP-TBS-10  
 Kumar Singha S.  
**EP35-436-24**  
 Kunihira L. OA-18-613-22  
 Kunihira B. EP18-275-22  
 Kunihira C. **EP20-295-23**  
 Kunzekwenyika C.  
**OA-17-605-22**  
 Kurada J.k. EP17-263-22  
 Kurbatova E. EP01-103-21  
 Kurniasari N.M.D.  
 OA-33-702-24  
 Kurniati N.M.  
 OA-33-702-24  
 Kusimo O. **OA-02-507-21**,  
**EP22-312-23**  
 Kutchukhidze G.  
 EP29-378-24  
 Kütt M. OA-31-691-23  
 Kuwatada J. **EP12-214-22**  
 Kuzhko M. OA-19-622-22  
 Kwabla M.P. **EP31-397-24**  
 Kwan A. OA-10-557-22,  
 OA-22-635-23,  
 OA-22-638-23  
 Kyaw K.W.Y. EP19-279-22  
 Kyi M.S. EP21-297-23  
 Kyokushaba J.  
 OA-37-731-24
- L**  
 Lachenal N. OA-41-753-24  
 LaCourse S. OA-01-501-21,  
 OA-01-506-21  
 LaCourse S.M. EP-TBS-22  
 Lalashowi J.M.  
 OA-03-519-21,  
 EP25-342-23  
 Lam C.K. OA-26-665-23,  
 OA-26-666-23,  
 EP26-352-23  
 Lam H. EP28-364-23  
 Lamunu M. OA-18-613-22  
 Lamunu D. EP02-115-21,  
 EP02-116-21  
 Lande H. OA-06-538-21  
 Lange C. TBS-OA-04,  
 EP-TBS-06, EP-TBS-50

- Langley I. EP16-258-22, EP19-278-22  
Laniado-Laborín R. EP-TBS-48, EP-TBS-83  
Largen A. EP07-164-21  
Larson E. **TBS-OA-02**  
Latif A. EP09-178-21  
Latorre I. **EP-TBS-03**  
Laurenson I.F. OA-03-517-21  
Laurenson I. EP36-451-24  
Lavanya J. OA-22-634-23  
Lavu E. OA-38-735-24  
Law I. OA-31-688-23  
Law S. **EP-TBS-80**  
Lawal O. EP34-433-24  
Lawanson A. EP06-152-21, EP08-172-21, EP12-216-22, EP18-273-22, EP19-281-22  
Laxmeshwar C. OA-24-653-23  
Le H. OA-36-723-24  
Le H.T. OA-36-726-24, EP31-399-24  
Leal-Calvo T. EP-TBS-24  
Leandro Andrade H. EP04-137-21  
Leavitt S. EP01-102-21  
LeBeau K. EP15-241-22  
Lebedeva I. EP29-379-24  
Lebina L. OA-15-594-22, OA-23-646-23  
Lebona L. EP16-255-22  
Leburu T. OA-03-515-21  
Lecca L.W. OA-33-703-24  
Lecca L. LB-2122-22, EP04-134-21, EP09-180-21, EP12-211-22, EP14-234-22, EP23-320-23, EP-TBS-02  
Lecca Garcia L. EP34-426-24  
Ledezma Almendras R. **EP14-232-22**  
Lee M.-R. OA-07-545-21, OA-07-548-21  
Lee C.-H. OA-07-545-21  
Lee W.-T. OA-25-656-23  
Lee J.S. OA-35-720-24  
Lee P.-H. EP06-154-21, EP22-309-23  
Lee P.H. **EP10-188-21**  
Lee S. EP-TBS-17, EP-TBS-27  
Lee H. **EP-TBS-27**  
Lehmann C. EP-TBS-07  
Leidianne Limirio Souza L. EP04-137-21  
Lemaire J.-F. **OA-02-512-21**, OA-23-643-23, **OA-41-747-24**, **EP07-159-21**, EP07-160-21, EP07-161-21  
Lemma D. EP18-276-22  
Leonard B. TBS-OA-08  
Leontieva S. **OA-04-527-21**  
Le Roux S. OA-09-554-21, **EP01-109-21**, EP05-148-21  
Leslie A. OA-24-647-23, EP-TBS-01  
Lesosky M. OA-40-744-24  
Lessells R. EP01-104-21  
Le T.H. EP22-314-23  
Leth F.v. EP11-201-22  
Letta T. EP13-221-22  
Letuba G.G. OA-15-594-22  
Levina K. OA-31-691-23  
Levy J. EP05-146-21, EP19-284-22  
Lewis J. **LB-2044-23**  
Li Q. OA-05-535-21, EP08-170-21  
Li L. OA-09-555-21  
Li X. **OA-11-563-22**, **EP08-170-21**  
Li C. OA-15-597-22  
Li T. OA-25-658-23  
Li W. LB-2070-24  
Li Y. **LB-2070-24**, LB-2070-24, EP-TBS-33  
Li J. EP08-170-21, EP10-195-21  
Li H. EP09-182-21  
Li N. EP13-229-22  
Li R. EP22-316-23  
Liabsuetrakul T. EP33-421-24  
Liang J. EP09-182-21  
Liao Q. EP10-195-21  
Lillebaek T. OA-24-650-23  
Lillis L. OA-05-530-21  
Lim H. **OA-12-575-22**  
Lim A.R. **OA-13-580-22**  
Lim J. LB-2127-24  
Limberis J. EP-TBS-33  
Limo J. EP24-326-23  
Lin P.-H. OA-25-656-23  
Lin C.Y.-C. OA-26-665-23  
Lin W.-H. OA-35-715-24  
Linas B. EP28-370-23  
Lindner A. LB-2093-22  
Lindy Dickson-Hall L. EP01-109-21  
Lineu Kritski A. OA-29-685-23, EP16-259-22  
Lingappa J.R. EP-TBS-22  
Lipman M.C.I. OA-04-522-21  
Lisboa V. EP-TBS-21  
Liu Y. OA-14-585-22, EP09-183-21, EP-TBS-86  
Liu Q. LB-1930-23  
Liu X. **EP04-133-21**, EP10-189-21, EP27-362-23  
Liu C.H. EP10-188-21  
Liu H. EP10-195-21  
Liverani M. LB-2071-23  
Llanos F. LB-2122-22  
Lo C. OA-32-697-24  
Lodaya J. EP33-418-24  
Lodi P. **EP17-267-22**, EP24-330-23  
Lofranco V. **EP01-103-21**  
Logue J. LB-2044-23  
Lokwani R. LB-2113-22  
Lomtadze N. OA-40-742-24  
Lone A. EP37-455-24, EP37-464-24  
Long A. OA-35-718-24  
Long R. EP02-113-21  
Long Q. EP04-136-21  
Long L.C. EP28-368-23  
Lonnroth K. OA-29-682-23  
Lönnroth K. EP13-225-22, EP22-315-23, EP28-368-23, EP29-382-24  
Lopes I. EP-TBS-21  
Lopes Rufino Alves R. EP-TBS-16, EP-TBS-24  
Lopez D.B.F. OA-13-583-22, OA-13-584-22  
Lopez D. OA-15-595-22, OA-18-616-22  
Lopez-Torrendon E. OA-13-580-22  
Lopez-Varela E. EP12-212-22  
Lourens M. EP02-115-21, EP02-116-21  
Lovadini V. EP04-137-21, EP19-282-22  
Loveday M. OA-09-554-21, EP01-109-21, EP05-148-21  
Lowary T.L. EP-TBS-38  
Lu P.-L. OA-07-548-21, EP-TBS-36  
Lu L. OA-32-694-24  
Lu F. LB-1930-23  
Lu P. LB-1930-23  
Lu W. LB-1930-23  
Luchini A. OA-05-533-21  
Luciano Giacomet C. EP04-137-21  
Luedtke S. **EP03-119-21**  
Lufesi N. EP25-339-23  
Luhanga D. OA-07-544-21, EP18-270-22  
Lukhele B. OA-21-631-22  
Lukoye D. EP18-275-22  
Lulu D. OA-36-722-24  
Lungu P. OA-25-657-23, **EP06-158-21**, EP21-303-23, EP23-323-23, EP30-388-24  
Luo H. OA-09-555-21, EP13-229-22, **EP22-317-23**, **EP34-427-24**  
Lusekelo J. EP26-344-23  
Lutz B.R. OA-05-531-21  
Lutz B. EP05-145-21  
Luu B.K. **OA-19-624-22**  
Lwanda L. EP15-242-22  
Ly S. EP33-425-24  
Lyimo J. EP20-293-23  
Lyland A. OA-01-501-21  
Lynch S. OA-10-562-22, OA-13-577-22, OA-15-593-22, OA-29-686-23, EP05-147-21  
Lytvynenko N. EP29-380-24
- M**  
Ma J. EP13-229-22, EP34-427-24  
Ma H. **EP27-362-23**  
Maama L. EP11-207-22  
Maartens G. OA-01-503-21, EP09-176-21  
Mabasa P. EP30-393-24  
Mabote L. EP10-196-21  
Mac T.H. OA-07-547-21, EP10-194-21  
Macadangang C. EP30-393-24  
Macalalad N. EP01-103-21  
Macaraig M. OA-26-665-23, OA-26-666-23, EP26-352-23  
Macharia S. EP37-465-24  
Machava R. EP24-327-23  
MacLean E. **EP19-285-22**  
MacPherson P. LB-2112-24, EP03-120-21, EP25-335-23, EP-TBS-40  
Macuacua B. **EP24-327-23**  
Madan J. EP16-258-22  
Madden N. EP32-411-24  
Madubu D.M. OA-23-640-23, EP14-235-22  
Madukaji L. **EP32-408-24**  
Mafeto M. EP21-300-23  
Mafort T. EP-TBS-21  
Mafukidze A. EP22-308-23  
Magalie N. EP15-246-22  
Magassouba A.S. EP13-220-22  
Magcaba Z.P. OA-05-531-21  
Magee M. OA-40-742-24  
Magee M.J. EP29-378-24  
Maghradze N. **OA-27-672-23**  
Magis-Escurra C. EP27-363-23  
Magomere R. EP17-267-22, **EP20-288-23**, **EP24-330-23**  
Mahapatra N.K. EP09-186-21  
Maharaj R. OA-37-732-24  
Mahub T. OA-12-573-22, **EP33-418-24**  
Mahmud R. EP08-168-21  
Mahto R. EP15-247-22  
Mai H.N.T. OA-28-674-23  
Maibvise C. **EP33-419-24**  
Maiello P. TBS-OA-02  
Maina A. OA-32-698-24  
Maina P. EP26-345-23  
Mainali R. OA-10-556-22  
Maingowa N. EP-TBS-54  
Majidulla A. EP25-338-23, **EP25-340-23**  
Majwala R. OA-15-592-22, EP30-390-24  
Majwala R.K. OA-25-660-23  
Makabayi Mugabe R. OA-12-571-22

- Makabayi-Mugabe R. EP01-106-21
- Makaka J. EP11-207-22
- Makara N. EP24-329-23
- Makgopa G. EP16-255-22
- Makhunga P. LB-2127-24
- Makolo D. OA-03-516-21
- Makone A. EP10-196-21
- Makouski M. EP29-383-24
- Makwenda C. EP25-339-23
- Malakyan K. EP29-380-24
- Malama K. OA-25-657-23, EP06-158-21, EP21-303-23, EP23-323-23, EP30-388-24
- Maleya P. **OA-10-559-22**
- Malhotra S. **OA-33-704-24**
- Malhotra A. **EP16-260-22**, EP20-296-23
- Malik A. OA-34-710-24
- Malik F. EP21-298-23
- Maliko S. OA-07-544-21, EP18-270-22
- Malin J.J. EP-TBS-07
- Malinga S. LB-2127-24
- Mallick G. **OA-21-626-22**, **EP09-186-21**, **EP15-239-22**, **EP15-249-22**
- Maloney S. EP21-302-23
- Mamatenko A. EP23-321-23
- Mambuque E. EP12-212-22
- Mamnoon F. EP01-105-21
- Mamuda K. OA-03-516-21
- Mamuka D. EP32-411-24
- Manabe Y. EP13-224-22
- Mandal A. OA-25-655-23
- Mandalakas A. OA-21-631-22, OA-41-751-24, EP12-213-22, EP-TBS-06
- Mandalakas A.M. OA-28-675-23, TBS-OA-04
- Mandishona T. EP-TBS-75
- Manduku V. EP25-335-23
- Mangan J.M. OA-26-665-23, OA-26-666-23, EP26-352-23
- Mangan J. EP02-115-21, **EP02-116-21**
- Mangeni R. **OA-22-637-23**, **EP34-431-24**
- Mangono T. **OA-22-634-23**
- Mangoro Z. EP34-433-24
- Manhiça I. OA-07-546-21, OA-28-678-23, EP24-327-23, EP28-375-23
- Manjhi R. EP-TBS-70
- Manley N. EP-TBS-62
- Mann N. OA-33-706-24
- Mannix S. LB-2047-21
- Mansoor H. EP01-105-21
- Mantell J.E. OA-09-552-21, EP22-308-23
- Mantsoki A. EP-TBS-38
- Manzoor L. **OA-41-749-24**, EP21-306-23
- Mao T.E. OA-23-641-23, EP33-425-24
- Mapamba D. OA-35-713-24
- Mapingure M. OA-09-552-21
- Mapuranga T. OA-07-546-21
- Maqbool N. OA-37-734-24
- Marangu D. OA-05-531-21
- Marazzi M.C. OA-05-529-21
- Marcelo D. EP19-278-22
- Marcy O. EP12-215-22
- Mar Diop Y. EP07-165-21
- Margineanu I. **OA-27-668-23**
- Marin M. **TBS-OA-12**
- Marks G.B. OA-19-624-22
- Marks G. EP25-341-23
- Maro P. OA-06-539-21
- Maro A. EP20-293-23
- Marokane P. **OA-16-599-22**
- Marquardt T. EP05-144-21
- Marquez N. **EP30-393-24**
- Martinez L. **LB-1930-23**
- Martinez Castro N. EP27-363-23
- Martinson N. OA-02-509-21, OA-02-513-21, OA-15-594-22, OA-23-646-23
- Maruri F. OA-24-647-23, EP-TBS-01
- Marwitz S. TBS-OA-04
- Marx F.M. **OA-21-632-22**, EP04-131-21
- Marx F. EP04-129-21, EP24-332-23
- Maryala B. EP31-395-24, EP31-401-24
- Masaba R. EP11-204-22
- Masese A. **OA-21-630-22**
- Masese L. EP24-331-23
- Masini T. OA-10-562-22, **OA-13-577-22**, OA-15-593-22, EP05-147-21, EP12-217-22
- Masini E. OA-13-577-22, **OA-15-593-22**, EP25-335-23
- Massawe I. EP26-344-23
- Masserey E. EP23-319-23
- Massou F. **EP19-283-22**
- Masuku S. **OA-01-502-21**, OA-01-505-21
- Masvawure T.B. OA-09-552-21
- Matallana M. EP-TBS-03
- Mate A. LB-2115-21
- Matechi E. OA-29-683-23
- Mathad J. EP27-357-23, EP30-386-24, **EP-TBS-10**, **EP-TBS-41**
- Mathee S. EP17-266-22
- Mathew M. **OA-26-663-23**
- Mathur T. EP33-418-24
- Matji R. EP16-255-22, EP21-300-23, EP21-305-23
- Matovu J. EP-TBS-61
- Matsenjwa M. OA-21-631-22
- Matta S. EP31-398-24
- Matteelli A. OA-28-673-23
- Mattoo S.K. EP07-161-21, EP32-413-24, EP33-423-24
- Matuta F. EP-TBS-54
- Matveeva M. EP13-223-22
- Maurer F.P. TBS-OA-04
- Maurer F. EP-TBS-50, EP-TBS-53
- mave V. OA-34-711-24
- Mave V. LB-2056-24, EP12-208-22, EP15-241-22, EP30-386-24, EP-TBS-15
- Mavhunga F. OA-16-604-22, EP19-284-22
- Mawandani R. OA-36-725-24, EP26-353-23
- Mayito J. EP16-252-22, EP18-274-22
- Mazahir T. EP30-387-24
- Mazed M.A. EP15-244-22
- Mazibuko M. OA-24-647-23, EP-TBS-01
- Mazivavose S. OA-17-605-22
- Mbassa V. OA-13-579-22, OA-32-698-24
- Mbatha M. OA-24-653-23, EP20-294-23
- Mbelele P.M. **EP34-435-24**
- Mbelele P. EP-TBS-76
- Mbendera K. EP14-231-22, EP14-236-22, EP14-238-22
- Mbewe W. EP30-388-24
- Mboizi R. EP15-241-22
- Mboya P. **EP11-204-22**
- Mbugua M. OA-16-601-22
- Mbugua L. EP24-331-23
- Mburu M. OA-16-601-22
- Mbuve C. EP31-400-24
- McCarthy K. EP11-206-22
- McCollum E.D. **OA-03-514-21**, **EP07-162-21**, **EP25-339-23**
- McCollum E. EP25-334-23
- McCreech N. OA-14-587-22
- McDermid J. LB-2119-21
- McGaugh L. OA-15-595-22, OA-18-616-22
- McGowan C. EP02-112-21
- Mchembere W. EP11-206-22
- McIlleron H. OA-41-752-24, EP09-176-21
- McKenna L. EP02-115-21, EP02-116-21, EP10-196-21
- McKerry A. TBS-OA-08
- Mckinn S. OA-36-726-24, EP31-399-24
- McQuaid C.F. OA-14-587-22, TBS-OA-07, EP28-373-23, EP-TBS-34
- McShane H. EP-TBS-13
- Mdala M. EP25-339-23
- Mduma E. OA-37-729-24, LB-2119-21
- Meaza A. OA-38-735-24
- Medvinskiy I. **EP-TBS-71**
- Meehan S.-A. OA-21-632-22, EP03-125-21, EP04-129-21, **EP04-131-21**
- Meghji J. OA-40-744-24
- Mehiri E. EP36-450-24
- Mehra S. EP12-214-22
- Meis M. EP05-140-21
- Mejja G. EP25-343-23
- Meka A. OA-23-642-23, EP12-209-22
- Meka A.O. EP07-166-21, EP14-233-22, EP37-461-24
- Melaku Z. OA-36-722-24
- Melenge S. OA-28-679-23
- Melgar M. **OA-32-698-24**
- Mello Schmidt C. EP-TBS-19
- Mema N. LB-2090-22
- Memani B. EP17-265-22
- Mendoza V. EP19-278-22
- Mendoza-Hisey E. **OA-36-721-24**
- Meneguim A.C. EP01-105-21
- Mensah G.I. EP-TBS-23, **EP-TBS-44**
- Menzies D. OA-07-542-21, EP02-113-21
- Menzies N. OA-32-694-24, EP28-373-23
- Menzies D. EP10-190-21
- Merabishvili T. EP29-378-24
- Meralli F. OA-36-721-24, OA-36-725-24, EP26-353-23
- Meredit S. OA-17-608-22
- Merker M. EP-TBS-50
- Merle C. EP07-165-21
- Messadi F. EP36-450-24
- Meya D.B. LB-1968-21
- Meyer A.J. **OA-12-572-22**
- Mhlaba T. OA-22-639-23
- M.H. Mitchell E. OA-12-576-22
- Migambi P. EP05-140-21
- Migwambo C. EP06-153-21, EP11-204-22
- Mihalic M. EP36-453-24
- Mihova R. EP06-158-21
- Mikiashvili L. TBS-OA-09
- Milanga M. EP10-196-21
- Milenge P. OA-01-500-21, OA-37-730-24
- Millard J. OA-17-609-22, OA-35-714-24
- Miller J. EP20-295-23
- Milliet J.-P. EP27-355-23
- Millones A.K. EP04-134-21, EP09-180-21, EP14-234-22

- Millones Gomez A.K. EP34-426-24
- Milovanovic M. OA-23-646-23
- Milsana K. EP01-109-21
- Mina J.G. EP26-351-23
- Minga G. OA-29-681-23
- Mingedi B. OA-29-681-23
- Minja L.T. OA-35-713-24
- Miotto P. **TBS-OA-11**
- Mirza A. OA-27-667-23
- Mishra S. OA-21-626-22, EP09-186-21, EP15-239-22
- Mishra G. **OA-31-690-23**
- Mishra R. EP15-247-22
- Misoï S. EP26-345-23
- Mistry N. OA-11-564-22, OA-25-655-23, TBS-OA-05
- Mitarai S. EP-TBS-38
- Mitchell E. EP06-152-21
- Miteni L. OA-37-730-24
- Mitnick C. EP-TBS-80
- Mitrani L. OA-09-554-21, EP01-109-21, **EP05-148-21**
- Mitropoulos N. EP26-352-23
- Mizernitsky Y. EP-TBS-09
- Mkalira K.E. **EP08-175-21**
- Mkhabela M. OA-21-631-22
- Mkhize J. EP20-294-23
- Mkhombo T. OA-10-557-22, OA-22-635-23
- Mlauzi L. EP14-230-22, **EP14-238-22**, EP21-301-23
- Mlaviwa M. EP25-336-23
- Mlisana K. OA-09-554-21, EP05-148-21
- Mmanga M. EP08-175-21, EP14-236-22, EP15-240-22
- M'manga M. **EP14-231-22**
- Mmbaga B. OA-24-650-23
- Mmile N. OA-02-513-21
- Mmolawa L. OA-02-509-21
- Mnesa B. OA-40-744-24
- Mockenhaupt F. LB-2093-22
- Moe M.M. OA-37-728-24
- Mofolo M. EP11-207-22
- Moh R. EP12-215-22
- Mohamed S. **EP-TBS-76**
- Mohammed Z. OA-03-516-21
- Mohanty S. OA-21-626-22, EP09-186-21, EP15-239-22, EP15-249-22
- Mohanty V. OA-33-704-24
- Mohapatra D. OA-21-629-22, EP14-237-22, EP33-417-24
- Mohd Hanafiah K. EP-TBS-20
- Mohr-Holland E. **LB-2090-22**, EP07-167-21, **EP17-265-22**, **EP17-266-22**
- Mohsin S.M.I. EP37-457-24
- Moiseeva E. EP11-197-22
- Mokrousov I. **OA-31-691-23**, EP29-379-24
- Molina-Pinargote I. EP27-355-23
- Molinasleon G. EP27-363-23
- Moll A. LB-2127-24
- Mom K. OA-23-641-23
- Mon A.S. OA-35-720-24
- Mondal R. **OA-11-568-22**, EP-TBS-47
- Monga F. OA-37-730-24
- Mongia H. **EP01-105-21**
- Monroe A. EP04-130-21
- Moodley S. OA-24-647-23, EP-TBS-01, EP-TBS-33
- Moon N. **EP22-313-23**
- Moonan P. EP26-344-23
- Moore D.A. OA-35-719-24
- Moore D.A.J. LB-2087-24
- Moosa M.-Y. OA-24-647-23
- Moosa M.-Y.S. EP-TBS-01
- Mora M. **EP33-425-24**
- Morales M.L. EP05-146-21
- Moran A. **EP16-255-22**, **EP21-300-23**
- Moreau E. LB-1903-23, EP-TBS-38
- Moreno-Molina M. **EP-TBS-49**, EP-TBS-51
- Moriarty R. TBS-OA-02
- Morishita F. EP28-366-23
- Morris L. EP26-346-23
- Mortimer K. OA-03-518-21, OA-03-520-21, OA-40-744-24
- Morton B. OA-03-518-21, EP25-335-23
- Moshabela M. OA-09-554-21, OA-13-578-22, EP01-109-21, EP05-148-21
- Mosneaga A. EP05-147-21, EP12-217-22
- Motlhaleng K. OA-01-502-21
- Motlhaoleng K. OA-01-505-21, **EP22-307-23**
- Motoku J. OA-01-504-21
- Moturi E. **OA-06-539-21**, OA-32-698-24
- Moyo S. OA-10-557-22, OA-22-635-23, **OA-22-638-23**, OA-22-639-23
- Moyo B. LB-2112-24
- Mpagama S.G. OA-24-648-23, EP34-435-24
- Mpagama S. OA-24-650-23, OA-37-729-24, LB-2119-21, EP-TBS-76
- Mpande C.A. TBS-OA-06
- Mpazanje R.G. OA-23-640-23, EP08-172-21, EP14-235-22
- Mphahlele M. EP21-300-23, **EP21-305-23**
- Mphasa N. OA-10-558-22
- Mpinda S. EP11-207-22
- Mpolya E.A. EP34-435-24
- Mpunga J. OA-10-558-22, EP08-175-21, EP14-230-22, EP14-231-22, EP14-236-22, EP14-238-22, EP15-240-22, EP15-242-22, EP15-243-22, EP21-301-23
- Mshali K. EP15-243-22
- Mshanga A. OA-06-539-21
- Msukwa M. OA-09-552-21
- Mtafya B. **OA-18-617-22**, TBS-OA-14, EP34-432-24, EP34-435-24
- Mtete E. EP26-344-23
- Mtotha - Nindi B. EP15-240-22
- Mtotha\_Nindi B. **EP15-242-22**
- Muchoro S. **EP16-252-22**
- Muchuro S. OA-15-592-22, **EP18-274-22**
- Mudiope M. OA-38-738-24
- Mueller L. OA-06-539-21
- Mueni E. OA-21-630-22
- Mugabe R. EP04-139-21
- Mugambi L. OA-19-620-22
- Mugambi - Nyaboga L. OA-21-630-22
- Mugi B. EP25-335-23
- Mugruza R. **OA-05-533-21**
- Muhumuza A. OA-09-550-21
- Muhwezi A. OA-15-595-22, OA-18-616-22
- Mujuni D. OA-25-660-23, EP36-452-24
- Mukiibi J. OA-24-652-23, OA-31-689-23
- Mukiibi M. EP13-219-22
- Mukiri N. OA-16-601-22
- Mukopathy S. EP24-327-23
- Mukuka L. OA-38-739-24
- Mukwanjagi S. OA-05-529-21
- Mulai M. OA-07-544-21, EP18-270-22
- Mulder C. OA-27-671-23
- Mulenga V. EP15-241-22
- Muliaditan M. EP-TBS-86
- Mullen S. EP13-221-22
- Müller M. TBS-OA-04
- Mulowa M. EP03-126-21
- Mulupi S. OA-03-521-21
- Mulyawan I.K.H. OA-33-702-24
- Mundunda H. EP19-284-22
- Munene K. OA-05-529-21
- Munene A. OA-22-633-23, EP24-326-23, EP26-345-23
- Munene A.G. **EP32-405-24**
- Mungai B. OA-03-521-21, OA-21-630-22, **EP25-335-23**
- Munguambe S. EP12-212-22
- Muñiz-Salazar R. **EP-TBS-48**, EP-TBS-83
- Munshi T. **EP02-110-21**
- Munuo G. **EP20-293-23**
- Mureithi L. EP20-290-23
- Muriel Moreno B. EP27-355-23
- Murithi C. OA-01-504-21
- Murphy-okpala N. EP12-209-22
- Murphy-Okpala N. **OA-23-642-23**, EP07-166-21, EP14-233-22, EP37-461-24
- Murray M.B. OA-33-703-24, EP-TBS-02
- Murray M. EP23-320-23
- Murry M. TBS-OA-03
- Murunga V. OA-03-521-21
- Musaazi J. EP01-106-21, EP04-139-21
- Musau S. EP11-206-22
- Mushili T. OA-07-544-21, EP18-270-22
- Musinguzi J. OA-15-592-22, EP13-219-22, EP15-248-22
- Musisi K. OA-25-660-23, EP36-452-24
- Musisi E. TBS-OA-14, EP34-432-24
- Musoke P. EP02-114-21
- Mustapha G. OA-03-516-21
- Musuka G. OA-09-552-21
- Musvosvi M. TBS-OA-06
- Mutaquihia C. OA-28-678-23
- Mutayoba B. OA-29-683-23
- Mutesasira K. **OA-13-582-22**, OA-13-583-22, OA-13-584-22, OA-14-590-22, OA-18-618-22, OA-22-636-23, OA-22-637-23, EP04-139-21, EP30-390-24, EP34-431-24
- Muthumohan R. EP-TBS-42
- Mutiti A. EP22-308-23
- Muttamba W. OA-09-551-21
- Mutua J. OA-22-633-23
- Mutungu L. OA-28-676-23, OA-28-677-23
- Muwonge A. OA-15-595-22
- Muyinda H. OA-09-551-21
- Muyoyeta M. OA-07-544-21, **LB-1903-23**, EP18-270-22, EP30-388-24, EP36-454-24

- Mvusi L. EP21-305-23,  
EP23-324-23  
Mwaba I. OA-07-544-21,  
EP18-270-22  
Mwale C. EP30-388-24  
Mwamba E. **OA-07-544-21**,  
EP18-270-22  
Mwamba M. OA-25-657-23  
Mwamsidu C.  
OA-22-633-23,  
EP24-326-23,  
**EP26-345-23**,  
EP32-405-24  
Mwangi P. OA-16-601-22  
Mwangi J. OA-16-601-22  
Mwangi E. EP11-204-22  
Mwansa-Kambafwile J.  
EP21-305-23  
Mwansambo C.  
EP25-339-23  
Mwanza W. **OA-25-657-23**,  
EP36-454-24  
Mwashumbe C.  
**EP08-169-21**  
Mwebe S. EP36-449-24  
Mwelwa C. OA-38-739-24  
Mwewa J. OA-25-657-23  
Mwirigi N. EP16-254-22  
Myers B. **OA-32-697-24**,  
EP22-318-23  
Myint Z. OA-35-720-24  
Myint K.A. EP09-185-21  
Myneedu V.P.  
OA-38-737-24, EP-TBS-39  
Mzyece J. OA-25-657-23,  
EP23-323-23
- N**  
Nabadda-Ndidde S.  
EP16-252-22,  
EP18-274-22  
Nabeta P. OA-11-565-22,  
OA-38-736-24  
Nabwire S. EP13-226-22  
Nahid P. EP-TBS-69  
Naidoo P. OA-23-646-23,  
EP04-129-21, EP23-324-23  
Naidoo C. **EP-TBS-33**  
Naik G. LB-2113-22  
Naik S. EP27-357-23,  
EP30-386-24, EP-TBS-41  
Naing A.Y. EP19-279-22  
Nair S. OA-13-577-22,  
EP12-217-22  
Nair D. EP01-100-21  
Nakabuye M. **OA-11-565-22**  
Nakafeero J. OA-38-738-24  
Nakaishi K. EP-TBS-36  
Nakanwagi F. OA-18-618-22  
Nakasolya O. OA-24-652-23  
Nakato H. OA-15-592-22,  
OA-22-636-23,  
**EP03-124-21**  
Nakaweesa A. EP13-219-22,  
EP15-248-22  
Nakawooya M.  
OA-09-550-21,  
EP16-252-22, EP18-274-22  
Nakaye M. EP36-449-24  
Nakibuuka S. OA-18-618-22  
Nakitende L. OA-15-595-22  
Nakonechnaya S. **EP-TBS-09**  
Nalugwa T. LB-2087-24,  
EP13-219-22,  
EP13-226-22, **EP15-248-22**  
Nalutaaya A.  
OA-24-652-23,  
OA-31-689-23  
Namale C. OA-18-613-22  
Namburi S. EP-TBS-43  
Namuwenge P.  
OA-15-592-22,  
OA-37-731-24  
Namwanje H.  
OA-13-582-22,  
OA-13-583-22,  
EP04-139-21  
Nanda B. OA-21-626-22,  
EP09-186-21, EP15-239-22  
Nangendo J. OA-12-572-22  
Nantale M. EP13-219-22,  
EP15-248-22  
Naqvi A.J. EP12-214-22  
Narvskaya O. EP29-379-24,  
EP34-434-24  
Natarajan G. OA-22-634-23  
Natarajan P.L. EP01-100-21  
Natarajan S. EP09-184-21  
Naureen F. EP15-245-22  
Naveed I. EP08-171-21  
Nayak B. EP15-239-22  
Ncube N. OA-32-698-24  
Ndaferankhande J.  
LB-2112-24  
Ndayizigiye M. EP11-207-22  
Ndiaye Touré K.  
EP07-165-21  
Ndlovu B. OA-21-631-22  
Ndlovu M. EP22-307-23  
Ndlovu L. **EP-TBS-01**  
Ndoi H. OA-05-529-21  
Ndume B. EP10-192-21,  
EP26-348-23,  
EP30-384-24,  
EP30-385-24,  
EP31-394-24,  
EP32-409-24  
Ndunda N. EP21-305-23  
Negin J. OA-36-726-24,  
EP31-399-24  
Nemes E. **TBS-OA-06**  
Net G. EP10-193-21  
Netea M.G. TBS-OA-01  
Neuhann F. EP-TBS-07  
Neumuller C. EP17-265-22  
Neves de Almeida I.  
OA-29-685-23,  
EP16-259-22  
Ng K.C.S. **EP-TBS-02**  
Ngam E. OA-17-609-22  
Ngambu N. EP17-266-22  
Nganga E. **OA-19-620-22**  
Ng'ang'a E. OA-21-630-22  
Ng'ang'a J.M.  
OA-22-633-23,  
**EP24-326-23**  
Ngema S. EP20-294-23  
Ngo Q.C. EP25-341-23  
Ngobeni K. **EP21-304-23**  
Ngoepe A.T. EP-TBS-01  
Ngowi B. OA-29-683-23  
Ngubane N. OA-17-610-22  
Nguhiu P. OA-29-681-23,  
OA-29-682-23  
Nguyen N.V. OA-07-547-21,  
OA-12-576-22,  
OA-28-674-23,  
EP10-194-21  
Nguyen H.B. OA-07-547-21,  
OA-12-576-22,  
OA-28-674-23,  
EP10-194-21  
Nguyen V.N. OA-19-624-22,  
EP25-341-23  
Nguyen B.H. OA-19-624-22  
Nguyen T.A. OA-19-624-22,  
EP25-341-23  
Nguyen V.S. OA-19-624-22  
Nguyen P.T. OA-19-624-22  
Nguyen L.H. OA-28-674-23  
Nguyen N.T.T.  
**OA-28-674-23**  
Nguyen T.-A.  
OA-36-723-24,  
OA-36-726-24,  
**EP22-314-23**,  
EP31-399-24  
Nguyen T.T. EP10-194-21  
Nguyen G.H. EP10-194-21  
Nguyen T.T. EP22-314-23  
Ngwane M.W.  
OA-05-531-21  
Nhamoyebonde S.  
EP-TBS-01  
Nhoueng S. EP18-272-22  
Nhung N. EP10-190-21  
Nhung N.V. EP-TBS-64  
Nicol M. OA-09-554-21,  
EP01-109-21, EP05-148-21  
Nicol M.P. EP-TBS-38  
Nie Q. **EP22-316-23**  
Niemann S. OA-25-655-23,  
OA-40-743-24, EP-TBS-50,  
**EP-TBS-53**  
Nightingale R.  
**OA-40-744-24**  
Nikolayevskyy V.  
OA-28-673-23  
Nikolenko T. EP-TBS-85  
Nilgiriwala K.  
OA-25-655-23  
Nimkar S. **EP12-208-22**  
Nimmo C. **OA-35-714-24**,  
EP01-104-21  
Nindi B. EP15-243-22  
Niño-Ramírez Y.  
OA-28-679-23  
Nirmal C.R. OA-11-568-22  
Nishiguchi T. EP-TBS-06  
Nishikiori N. EP28-366-23  
Nishkiori N. OA-29-683-23  
Nitschkowski D. TBS-OA-04  
Niwagaba P. OA-15-595-22  
Niward K. OA-17-607-22,  
EP34-430-24  
Njoroge A. OA-01-504-21  
Njuguna S. OA-01-504-21  
Nkiere N. OA-29-681-23  
Nkiligi E. OA-29-683-23  
Nkirote W. EP24-326-23,  
EP32-405-24  
Nkolo A. OA-09-550-21,  
OA-12-571-22,  
OA-13-582-22,  
OA-13-583-22,  
OA-13-584-22,  
OA-14-590-22,  
OA-15-592-22,  
OA-18-618-22,  
OA-22-636-23,  
OA-22-637-23,  
EP01-106-21,  
EP18-274-22,  
EP30-390-24,  
EP34-431-24  
Nkombe E. EP24-333-23  
Nkosi S. OA-02-513-21  
Nkulu A. OA-01-500-21  
Nkwane Y. EP16-255-22  
Nliwasa M. LB-2112-24,  
EP03-120-21, EP-TBS-40  
Noeske J. OA-13-579-22,  
EP33-420-24  
Nongo D. EP08-172-21,  
EP10-192-21,  
EP31-394-24,  
EP32-409-24  
Nonyane B.A.  
OA-23-646-23  
Noori T. OA-27-668-23  
Nordqvist D. OA-17-607-22  
Noreen N. **EP08-171-21**  
North A. OA-22-638-23  
Norzin T. EP05-149-21  
Noursadeghi M.  
EP-TBS-33  
N P A. EP15-247-22  
Nsanja P. EP20-295-23  
Nsawotebba A.  
**OA-25-660-23**,  
OA-37-731-24,  
EP36-452-24  
Nsereko M. OA-11-565-22,  
OA-38-736-24  
Nsona H. EP15-240-22  
Nsubuga Nyombi T.  
OA-12-571-22,  
OA-22-637-23,  
EP30-390-24, EP34-431-24  
Ntinginya N.E.  
OA-03-519-21,  
OA-40-743-24,  
TBS-OA-14, EP22-315-23,  
EP25-342-23,  
EP28-368-23,  
EP34-432-24  
Ntinginya N. **OA-35-713-24**  
Ntogwisangu F.  
EP20-293-23  
Ntsele P. EP21-305-23  
Ntudhu S. OA-18-618-22  
Nuermberger E. TBS-OA-13,  
TBS-OA-16, EP-TBS-67,  
EP-TBS-82  
Nugent R. OA-33-706-24

- Nwadike P. EP19-281-22, EP34-433-24  
 Nwafor C.C. OA-23-642-23, EP12-209-22  
 Nwafor C.C. EP07-166-21, EP14-233-22, EP37-461-24  
 Nwagagbo F. OA-10-560-22, OA-19-623-22, OA-36-724-24, EP16-261-22, EP17-268-22, **EP37-456-24**  
 Nwaokoye N. EP10-192-21, EP26-348-23, EP30-384-24, EP31-394-24, EP32-409-24  
 Nwokoye N. OA-14-588-22, OA-16-603-22, EP19-280-22, **EP19-281-22**, **EP34-433-24**, EP36-447-24  
 Nwongbouwoh Muefong C. **EP-TBS-11**, **EP-TBS-12**  
 Nyaboke D. **EP37-465-24**  
 Nyaga D. EP31-400-24  
 Nyangaresi M. EP37-465-24  
 Nyangu S. **EP18-270-22**, EP30-388-24  
 Nyang'wa B.-T. OA-32-700-24  
 Nyawo G. EP-TBS-33  
 Nyegenye W. EP16-252-22, EP18-274-22  
 Nyimbili S. EP21-303-23, EP23-323-23, **EP30-388-24**  
 Nyinoburyo R. **OA-15-595-22**, **OA-18-616-22**  
 Nyirenda G. **OA-10-558-22**  
 Nyirenda A. EP20-293-23  
 Nyombi A. OA-25-660-23, OA-37-731-24, EP34-431-24, EP36-445-24  
 Nyondo B. OA-38-739-24  
 Nyunt W.W. OA-35-720-24  
 Nzawa R. EP03-120-21, EP-TBS-40
- O**  
 Obanubi C. OA-10-560-22, OA-36-724-24, EP16-261-22, EP17-268-22, EP37-456-24, EP37-458-24  
 Obasi A. OA-03-521-21  
 Obeng J. EP02-113-21  
 Ocerro A. EP03-124-21, EP30-390-24  
 Ochanda P.N. EP16-252-22  
 O-Chi R. EP30-393-24  
 Ochoa-Teran A. EP-TBS-83  
 O'Connor S. TBS-OA-02  
 Odhiambo A. OA-01-501-21  
 Odionyi J. EP11-204-22  
 Odone A. OA-31-688-23  
 O'Donnell M. OA-06-540-21, OA-35-714-24  
 O'Donnell M.R. OA-12-573-22  
 Odume B. OA-10-561-22, **OA-14-588-22**, OA-16-603-22, EP09-179-21, EP10-187-21, EP11-199-22, EP19-280-22, EP19-281-22, EP19-286-22, EP24-333-23, EP31-403-24, EP32-404-24, EP32-406-24, EP32-407-24, EP34-433-24, EP36-447-24  
 Odusote T. OA-10-560-22, OA-36-724-24, EP08-172-21, EP13-222-22, EP16-261-22, EP18-273-22, EP32-412-24, EP37-456-24, EP37-458-24  
 Oelofse S. **OA-17-610-22**  
 Ofuche E. EP32-408-24  
 Ogarkov O. EP11-197-22, EP-TBS-72  
 Ogayse S. **EP37-460-24**  
 Ogbudebe C. OA-10-561-22, OA-14-588-22, EP10-187-21, **EP10-192-21**, EP19-280-22, EP19-281-22, **EP26-348-23**, **EP30-384-24**, **EP30-385-24**, **EP31-394-24**, EP32-406-24, **EP32-409-24**  
 Ogiri S. EP14-235-22  
 Oh B. EP22-313-23  
 Ohiembor H. EP30-385-24  
 Ohkado A. EP33-424-24  
 Ohler L. OA-24-653-23, **EP13-228-22**, **EP20-294-23**  
 Ojo E. EP32-408-24  
 Okada M. **EP-TBS-60**  
 Okal D. EP06-153-21  
 Okamoto E. EP18-272-22  
 Okekearu I. OA-19-623-22, EP16-261-22, EP17-268-22, EP32-406-24, EP37-456-24, EP37-458-24  
 Okoko G. OA-22-633-23, EP24-326-23  
 Okonkwo F. OA-19-623-22, EP17-268-22  
 Okonkwo P. EP32-408-24  
 Okumu A. EP11-206-22  
 Okwalinga T. OA-06-537-21  
 Olarewaju O. EP18-273-22  
 Olaru I.D. TBS-OA-04  
 Olashore E. OA-19-623-22, EP17-268-22  
 Olemukan R. EP18-277-22  
 Olinger G. EP-TBS-52  
 Oliva Rapoport V. **EP12-211-22**  
 Oliveira Hashiguchi L. **LB-2071-23**  
 Olivier S. EP32-410-24  
 Olowe O..A. OA-24-653-23  
 Olusola A. EP06-152-21  
 Olusola-Faleyeye B. OA-10-560-22, OA-10-561-22, OA-19-623-22, OA-36-724-24, **EP16-261-22**, EP17-268-22, EP37-456-24, EP37-458-24  
 Omar S. EP21-305-23  
 Omar A. EP25-340-23  
 Omer A. EP18-276-22  
 Omondi E. OA-10-559-22  
 Omoniyi F.A. OA-23-640-23, **EP08-172-21**  
 Omoniyi A. EP13-222-22, EP18-273-22, EP30-392-24  
 Omoniyi A.F. EP14-235-22  
 Omosebi O. EP18-273-22  
 Omulo S. **EP06-153-21**  
 On'gan'go J. OA-29-682-23  
 Ong'ang'o J. EP16-254-22  
 Ongareno P. **OA-06-537-21**  
 Onitiju L. EP16-256-22  
 Onoh M. OA-03-516-21, EP20-289-23  
 Onoh M.O. OA-23-640-23, EP14-235-22  
 Onozaki I. OA-31-688-23, EP09-185-21  
 Onuoha M. **OA-36-727-24**, EP24-333-23, EP31-403-24  
 Onyango D. OA-01-501-21, **OA-01-506-21**  
 Onyango E. OA-16-601-22, OA-19-620-22, OA-21-630-22, EP37-465-24, EP-TBS-66  
 Onyima A. **OA-23-644-23**  
 Onzere L. OA-16-601-22  
 Oo T.N. EP30-391-24  
 Oo M.M. **EP33-421-24**  
 Oosthyuzen W. EP-TBS-61  
 Opanga B. OA-05-529-21  
 Oprunenco A. EP05-151-21  
 Opwaka H. OA-16-601-22  
 Orangi S. EP16-254-22  
 Oreskovic A. **OA-05-531-21**
- Orillaza-Chi R. **EP26-351-23**  
 Ork C. OA-12-570-22, EP13-227-22  
 Orlando S. OA-05-529-21  
 Orne-Gliemann J. EP12-215-22  
 Oronje R. OA-03-521-21  
 Orrell C. OA-06-540-21  
 Ortuño-Gutiérrez N. EP13-220-22, EP14-232-22  
 Osberg M. OA-09-550-21  
 Osman M. OA-21-632-22, EP03-125-21, **EP04-129-21**, EP04-131-21, EP23-324-23  
 Ossai E. EP07-166-21  
 Oswal V. TBS-OA-05  
 Otero L. OA-40-745-24, OA-40-746-24  
 Otieno K. EP11-206-22  
 Otieno-Masaba R. **OA-02-508-21**, OA-02-510-21  
 Otuba J.P. OA-13-582-22, **OA-13-583-22**, **OA-13-584-22**  
 Otuba J. OA-14-590-22  
 Ouma M. OA-02-508-21, OA-02-510-21  
 Oundo C. OA-22-637-23  
 Oussenko I. TBS-OA-12  
 Owiti P. EP-TBS-66  
 Owolabi O. EP-TBS-11, EP-TBS-12  
 Owolagba F. EP32-408-24  
 Owour K. OA-19-620-22  
 Owusu E. EP-TBS-23  
 Oxlade O. **EP02-113-21**  
 Oyama E. EP08-172-21  
 Oyando R. EP16-254-22  
 Oyediran K. OA-09-551-21, **EP13-221-22**  
 Oyewusi L. **EP11-207-22**  
 Oyuku D. EP13-219-22, EP15-248-22  
 Ozoh U. OA-03-520-21  
 Ozório Moraes M. EP-TBS-24
- P**  
 Pacala D. OA-28-678-23  
 Padayatchi N. OA-06-540-21, OA-12-573-22, OA-35-714-24  
 Padoko C. EP14-230-22  
 Pai M. OA-10-557-22, OA-22-635-23, OA-22-638-23  
 Pakhlaonova A. **EP-TBS-63**  
 Palacios V. OA-28-679-23  
 Palaniyandi K. **OA-34-708-24**  
 Palendira U. EP-TBS-29  
 Palha P. EP04-130-21  
 Palicpic C. EP28-371-23



- Palmer M. OA-11-566-22, EP02-112-21, EP15-241-22  
 Palmer T. EP28-375-23  
 Palmer Z. EP-TBS-33  
 Palomino S. LB-2122-22  
 Palukani-Masiye W. OA-38-739-24  
 Pambudi I. EP01-108-21  
 Pan H. TBS-OA-03, LB-1930-23  
 Panda B. OA-21-626-22, EP09-186-21, EP15-239-22  
 Panda A. OA-21-629-22, EP14-237-22, EP33-417-24  
 Pande T. OA-10-556-22, EP03-118-21, EP21-298-23, EP34-428-24  
 Pande P. OA-26-664-23  
 Pandey S.K. OA-06-538-21  
 Pandey P. OA-26-663-23, EP03-127-21  
 Pang J. OA-35-714-24  
 Panibatla V. OA-06-536-21, EP26-350-23, **EP31-395-24**, **EP31-401-24**, EP33-415-24, EP33-416-24  
 Panigrahi S. EP-TBS-70  
 Panpradist N. OA-05-531-21  
 Pant A. LB-2113-22, EP-TBS-74  
 Pantoja A. OA-29-683-23  
 Papineni S. **OA-09-553-21**, **EP03-121-21**  
 Paradkar M. EP-TBS-15  
 Paredes-Martinez A. EP-TBS-48  
 Pareek M. OA-27-668-23  
 Parihatin A. EP01-108-21  
 Parija D. EP37-464-24  
 Park A.Y. OA-32-699-24  
 Park M. EP22-313-23  
 Park S. EP22-313-23  
 Park Y. **EP-TBS-77**, **EP-TBS-78**, **EP-TBS-79**  
 Parmar M. EP03-127-21  
 Parrish N. EP-TBS-52  
 Parvez M.M. EP-TBS-77  
 Pasha A. **OA-37-734-24**  
 Patel S.M. **OA-03-515-21**, **EP25-337-23**  
 Patel P. OA-09-553-21  
 Patel L. OA-17-606-22, EP02-111-21  
 Patel S. OA-36-722-24  
 Patel M.R. **EP18-275-22**  
 Patel M.Z. EP25-337-23  
 Pathri R. **EP-TBS-25**  
 Patil S. **EP-TBS-26**, **EP-TBS-46**  
 Patkar D. LB-2113-22  
 Patnaik B. OA-21-626-22, EP09-186-21  
 Patnak B. EP15-239-22  
 Patrobas P.D. OA-23-640-23, EP14-235-22  
 Patrobas P. EP08-172-21  
 Patterson B. **TBS-OA-08**  
 Paues J. OA-17-607-22  
 Pavlenko O. OA-04-523-21, OA-04-526-21  
 Pavlov V. EP29-379-24  
 Pavlova O. **OA-04-523-21**, **OA-04-526-21**  
 Paxton W. OA-37-733-24  
 Pearson C. OA-14-585-22  
 Pechinsky D. EP29-383-24  
 Pedro M. EP37-458-24  
 Peetluk L. OA-24-647-23, EP-TBS-01  
 Pei Y. EP09-183-21  
 Peinado J. LB-2122-22  
 Peloquin C. OA-37-729-24, TBS-OA-09  
 Pelton S.I. OA-03-515-21  
 Pelzer P.T. **EP05-140-21**, **EP-TBS-64**  
 Penninah Sekadde M. OA-38-738-24  
 Pennington S. OA-37-733-24  
 Pennington J. EP06-157-21  
 Penn-Nicholson A. **OA-38-735-24**, **OA-38-737-24**  
 Perea-Jacobo R. EP-TBS-48, **EP-TBS-83**  
 Pereira L. EP24-327-23  
 Pereira G. EP-TBS-21  
 Perera M. EP35-441-24, EP35-442-24, EP35-443-24, EP35-444-24  
 Perera C. **EP35-441-24**, **EP35-442-24**, **EP35-443-24**, **EP35-444-24**  
 Pérez-Porcuna T.M. OA-05-532-21  
 Periyannan D. EP35-441-24, EP35-442-24  
 Perrault A. LB-2115-21  
 Perrin C. **OA-10-562-22**  
 Persian R. EP05-151-21  
 Perumal N. EP29-376-24  
 Pescarini J. OA-31-693-23  
 Peterson D. **OA-02-511-21**  
 Petrenko V. EP23-321-23  
 Pfaff C. LB-2090-22  
 Pham T.H. OA-12-576-22  
 Pham N.Y. EP25-341-23  
 Pham D.C. EP22-314-23  
 Phap T. EP10-190-21  
 Phate S. EP11-207-22  
 Philip A. OA-06-538-21  
 Phillips P. TBS-OA-15, EP-TBS-69, EP-TBS-73  
 Phillips P.P. EP34-435-24  
 Phiri T. EP25-339-23  
 Phyu W.E. **OA-35-720-24**  
 Phyu M.H. **EP21-297-23**  
 Pidverbetska O. EP11-200-22  
 Pinheiro Victor de Araújo S.R. **EP-TBS-16**  
 Pinsker E. EP26-344-23, EP26-347-23  
 Pinter A. EP-TBS-38  
 Pinto I. EP04-130-21  
 Piubello A. OA-13-579-22  
 Plesnik S. EP36-453-24  
 Plisova T. EP-TBS-38  
 Plum C. **OA-03-520-21**  
 Plum G. EP-TBS-07  
 Pluvier Duarte Costa C. **EP-TBS-19**  
 Pola R. **EP-TBS-66**  
 Pollakis G. OA-37-733-24  
 Ponnighaus J. OA-34-712-24  
 Poojari V. OA-11-564-22  
 Popa C. TBS-OA-04  
 Porto Amadeu T. EP-TBS-16  
 Post E. OA-36-725-24, EP01-108-21, EP26-353-23  
 Pothal S. EP-TBS-70  
 Potluri R. EP28-371-23  
 Potty R. **OA-06-536-21**, **EP33-415-24**, **EP33-416-24**  
 Powers R. EP05-146-21  
 Pozmogova G. EP-TBS-85  
 Prabakaran L. OA-16-600-22  
 Pradhan E. EP28-375-23  
 Pradhan N. EP30-386-24  
 Prakash P. OA-22-634-23  
 Pranav P. OA-18-612-22  
 Prat-Aymerich C. EP27-355-23  
 Prem K. OA-18-614-22  
 Priesner V. EP-TBS-07  
 Pring L. EP33-425-24  
 Protti-Zanatta S. EP04-130-21  
 P. Sekadde M. OA-29-687-23  
 P. Solans B. **EP-TBS-65**  
 Puma D. LB-2122-22, EP04-134-21, EP09-180-21, EP14-234-22  
 Puma Abarca D.V. **EP34-426-24**  
 Punggrassami P. EP33-421-24  
 Purchase S. **OA-02-513-21**  
 Purwar P. **EP-TBS-39**  
 Püsken M. EP-TBS-07  
 Puyén Z.M. **OA-35-719-24**  
 Pym A.S. EP-TBS-01
- Q**  
 Qader G.Q. OA-16-602-22  
 Qader G. OA-41-749-24, **EP21-306-23**  
 Qawiy I. **OA-17-606-22**  
 Qin Z.Z. EP16-251-22, EP21-298-23  
 Quach T. OA-15-597-22, OA-26-661-23  
 Quadir A. EP21-298-23  
 Quan D. EP-TBS-29  
 Queiroz A. EP-TBS-41  
 Quincer E. **OA-01-501-21**  
 Quinn F. OA-15-597-22, OA-34-707-24, EP-TBS-62  
 Quinn T. OA-37-732-24  
 Quinn C.M. **LB-1968-21**  
 Quinones M. OA-19-625-22, EP-TBS-55
- R**  
 Rabe Carvalho F. EP-TBS-19  
 Rabie H. OA-41-752-24  
 Rabkin M. OA-09-552-21  
 Rachow A. OA-03-519-21, **OA-40-743-24**, TBS-OA-04, EP25-342-23, EP-TBS-11, EP-TBS-12  
 Radebe M. OA-16-599-22  
 Rader B. **EP03-123-21**  
 Radtke K.K. **OA-17-611-22**  
 Radtke K. EP-TBS-82  
 Ragan E.J. OA-32-697-24, EP22-318-23  
 Ragan E. EP01-102-21  
 Rahman M.M. OA-41-748-24, OA-41-748-24  
 Rahman M.T. **OA-41-748-24**  
 Rahmani L. EP21-306-23  
 Rahmawati S. EP01-108-21  
 Rai V. **OA-06-538-21**  
 Rai R. EP09-184-21  
 Raichur P. OA-34-711-24  
 Raihan S.M.G. EP33-422-24  
 Raisani S.A. EP21-298-23  
 Raj D. OA-34-708-24  
 Raj S. EP37-459-24  
 Rajaram1 M. LB-2110-24  
 Rajasuriya M. EP35-441-24, EP35-442-24, EP35-443-24, EP35-444-24  
 Rajendran P. **EP-TBS-47**  
 Rajpurkar K. EP21-302-23  
 Ramachandran R. OA-26-663-23, EP05-141-21, EP05-143-21, EP32-413-24, EP33-423-24  
 Ramachandran P.S. LB-1968-21  
 Ramachandran G. EP01-100-21  
 Rameshkumar S. EP01-100-21  
 Ramirez C. LB-2122-22  
 Ramos A.C.V. EP01-101-21  
 Ramos A. EP04-130-21, EP19-282-22  
 Ramos Adrian R.N. EP14-232-22  
 Randall A. EP-TBS-13  
 Randerer-Rees S. EP01-104-21

- Rangaka M. OA-01-503-21, OA-28-673-23  
Ranganathan R. OA-21-629-22, EP14-237-22, **EP33-417-24**  
Range N. OA-29-683-23  
Rangisetty S. EP07-161-21  
Rao P. LB-2119-21, **EP-TBS-72**, EP-TBS-76  
Rao R. EP03-121-21, EP05-143-21, EP15-250-22, EP28-365-23  
Rao T. EP03-121-21  
Rashid A. OA-05-530-21, **EP15-245-22**  
Rassool M.S. OA-40-743-24  
Ravanan P. EP03-127-21  
Ravenscroft L. EP05-151-21  
Ravi S. EP01-105-21, EP33-418-24  
Rawls J.F. EP25-337-23  
Ray Chaudhury M. OA-26-663-23  
Raymond L. EP01-103-21  
R. Barer M. EP27-354-23  
Realpe T. EP25-343-23  
Redd A. OA-37-732-24  
Reddy T. OA-01-502-21, OA-01-505-21  
Reddy R. EP33-416-24  
Redfern A. EP12-210-22  
Redwood L. **OA-12-576-22**  
Reed J.M. OA-14-587-22  
Reed M. OA-29-680-23  
Reena K. **OA-16-598-22**  
Reeve B. EP-TBS-33  
Refaya A.K. OA-34-708-24  
Rehan R. EP28-367-23  
Rehr M. OA-13-577-22, EP05-147-21  
Reichmuth M.L. **OA-13-581-22**  
Reichmuth M. **OA-35-716-24**  
Reid A. EP05-151-21  
Reimann M. TBS-OA-04, EP-TBS-50  
Reja M. EP06-157-21  
Reja S. EP37-457-24  
Ren F. EP13-229-22, EP34-427-24  
Ren W. EP-TBS-59  
Restrepo B.I. LB-2110-24  
Reuben M. EP25-336-23  
Reuß A. OA-27-670-23  
Reuter A. EP07-167-21, EP17-265-22, EP17-266-22  
Reynolds S. OA-37-732-24  
Reza T. OA-11-565-22, OA-38-736-24, OA-38-738-24, **EP13-219-22**, EP15-248-22  
Reza T.F. LB-2087-24  
Reza S. EP15-244-22  
Ribeiro-Alves M. EP-TBS-21  
Rich M. EP-TBS-80  
Richard J. LB-2047-21  
Richards A.S. OA-31-688-23, TBS-OA-07  
Richardson L. OA-26-662-23, EP03-118-21  
Richardson C. EP12-210-22  
Richardson B.A. EP-TBS-22  
Rickman H. OA-02-509-21  
Ricks S. **EP28-372-23**  
Ridhi S. EP15-247-22, **EP37-462-24**  
Rifat M. **EP08-168-21**, EP15-244-22, EP17-264-22, EP33-422-24, EP37-457-24  
Rifat I.A. EP17-264-22, **EP37-457-24**  
Rigouts I. EP19-283-22  
Robbe-Austerman S. OA-34-707-24  
Roberts T. OA-29-686-23  
Roberts J. **OA-37-732-24**  
Robinson E. OA-26-666-23  
Robledo J. EP25-343-23  
Robsky K. OA-24-652-23  
Roca M. OA-05-533-21  
Rocha Carvalho M.J. OA-29-685-23, EP16-259-22  
Rochat G. EP23-319-23  
Roche S. EP12-211-22  
Rodgers M. TBS-OA-02  
Rodrigues C. OA-38-735-24, OA-38-737-24  
Rodrigues L. EP-TBS-21  
Rodriguez C. **OA-25-658-23**  
Rodriguez S. OA-40-745-24, OA-40-746-24  
Roederer M. TBS-OA-02  
Rogers T. EP36-451-24  
Roggi A. EP13-220-22, EP23-319-23  
Rohr S. EP-TBS-07  
Rojas-Zúñiga C.N. OA-28-679-23  
Rolim Scholze A. EP04-137-21  
Rolling T. TBS-OA-04  
Romancenco E. EP36-453-24  
Romano F. **EP-TBS-86**  
Romanowski K. OA-07-542-21  
Ronge L. **OA-28-675-23**  
Rono A. OA-29-682-23  
Ronoh A. OA-05-529-21  
Rooney J. OA-32-697-24, EP09-177-21, EP22-318-23  
Rosapep L. **OA-10-560-22**, OA-36-724-24  
Roscoe C. EP19-284-22  
Rosen S. EP22-315-23, EP28-368-23  
Rosenthal A. OA-05-534-21, OA-19-625-22, OA-35-718-24, EP-TBS-49, EP-TBS-55  
Rosomakha O. EP-TBS-14  
Ross J. **OA-01-503-21**  
Ross C. OA-36-722-24  
Rossetti M.L.R. EP-TBS-37  
Rosslee M.-J. EP26-349-23  
Rosu L. **EP16-258-22**  
Roth B. EP26-344-23  
Roy A. OA-03-514-21, **OA-27-667-23**, EP25-334-23  
Roy T. OA-41-748-24, EP06-157-21  
Rozot V. TBS-OA-06  
Ruan Y. EP22-316-23  
Rubinstein F. EP05-145-21, **EP22-311-23**  
Rudgard W.E. EP04-138-21  
Rueda J. EP25-343-23  
Rufino R. EP-TBS-21  
Ruggiero A. OA-37-733-24  
Ruhwald M. OA-38-737-24, OA-38-741-24, LB-1903-23  
Ruiz-Cabello J. OA-05-532-21, EP27-355-23  
Ruiz-Tamayo P.S. EP-TBS-48  
Ruperez M. **EP20-290-23**  
Rupprechter S. EP-TBS-61  
Rusen A. EP02-111-21  
Ruslami R. EP02-113-21  
Russell T. OA-14-585-22  
Rustage K. OA-27-668-23  
Rusumba O. OA-23-645-23  
Ruswa N. OA-16-604-22, **EP19-284-22**  
Rutter L. EP10-196-21  
Ruvwa L. OA-09-551-21  
Rybak N. EP23-321-23  
Rybniker J. TBS-OA-04, EP-TBS-07  
Rylance J. OA-03-518-21, OA-40-744-24, EP25-336-23  
Rylance S. OA-40-744-24
- S**  
Saad N.J. **OA-27-670-23**  
Saavedra M.A. OA-24-654-23  
Saavedra B. EP12-212-22  
Sabi I. OA-03-519-21, OA-18-617-22, EP25-342-23  
Sabiiti W. OA-03-517-21, OA-18-617-22, OA-25-659-23, OA-35-713-24, **TBS-OA-14**, EP34-429-24, **EP34-432-24**, EP34-435-24  
Sachdeva K. OA-16-598-22  
Sachdeva K. OA-16-600-22  
Sachdeva K.s. OA-26-663-23  
Sachdeva K.S. EP05-141-21, EP05-143-21, EP28-365-23, EP32-413-24, EP33-423-24  
Sacks J. **LB-2093-22**, **LB-2100-22**  
Saeed S. EP25-338-23, EP25-340-23  
Safdar N. EP37-463-24  
Safi D.A. **OA-16-602-22**, OA-41-749-24  
Sah R. **OA-10-556-22**  
Saha A. **EP-TBS-22**  
Sahoo K.C. EP-TBS-70  
Sahu S. OA-13-577-22, OA-15-593-22, EP05-147-21  
Saito T. EP-TBS-60  
Sakamoto K. EP-TBS-62  
Salau O. EP26-348-23, EP30-385-24  
Saleem G. EP25-340-23  
Saleh S. **OA-03-518-21**  
Salerno M. OA-26-665-23, EP02-115-21, EP02-116-21  
Salerno M.M. OA-26-666-23, **EP26-352-23**  
Salfinger M. TBS-OA-12  
Salindri A. **OA-40-742-24**  
Salman S. EP25-340-23  
Salomon A. **OA-10-557-22**, OA-22-635-23, OA-22-638-23  
Saludar N.R. OA-24-654-23  
Salzer H.J.F. TBS-OA-04  
Samadi M.N. OA-41-749-24  
Sambakunsi H. OA-03-518-21  
Sampson D. EP26-346-23  
Samuels J. EP32-408-24  
Samungole G. EP36-454-24  
San C.C. OA-37-728-24, EP09-185-21, EP21-297-23  
Sanchez-Carballo P. TBS-OA-04, EP-TBS-50  
Sande E. EP18-275-22  
Sangsayunh P. **EP-TBS-31**  
Sani U. EP06-156-21, EP30-384-24  
Sanjurjo M. EP05-145-21  
Sankar R. **OA-18-612-22**  
Sanne I. EP22-315-23  
Sannino L. EP05-144-21  
Santiago M.R. EP26-351-23  
Santiveri C.M. OA-05-532-21  
Santos F.L. EP01-101-21, EP36-446-24  
Santos A.P. **EP-TBS-21**  
Santos-Lázaro D. OA-35-719-24  
Santos Neto M. EP04-130-21  
Sanyu A. OA-18-613-22  
Saoji K. EP-TBS-74  
Sarraf S. EP18-272-22  
Sariko M. EP-TBS-76  
Sarin S. OA-16-598-22  
Sarin S. OA-16-600-22, EP37-455-24

- EP37-464-24  
Saroufim\* M. **LB-2047-21**  
Satapathy J. EP09-186-21  
Sathi C. OA-26-666-23,  
EP26-352-23  
Sauli E. EP34-435-24  
Savic R.M. OA-17-611-22  
Savic R. TBS-OA-13,  
TBS-OA-15, TBS-OA-16,  
EP-TBS-65, EP-TBS-67,  
EP-TBS-69, EP-TBS-73,  
EP-TBS-81, EP-TBS-82,  
EP-TBS-84  
Sayedi S.M. OA-16-602-22,  
OA-41-749-24  
Scanga C. TBS-OA-02  
SchAAF H.S. OA-17-611-22,  
**EP12-210-22**,  
EP23-324-23  
Schaap A. EP20-290-23  
Schaub D. TBS-OA-04,  
EP-TBS-50  
Schluger N.W.  
OA-26-665-23  
Schneider H. OA-13-578-22  
Scholten J. EP19-281-22  
Schön T. OA-17-607-22,  
EP34-430-24  
Schreurs I. EP10-193-21  
Schubert P.T. EP12-210-22  
Schuhmann M. TBS-OA-04  
Schumacher S.G.  
OA-38-735-24,  
OA-38-737-24, EP-TBS-38  
Schumacher S.  
OA-38-741-24, LB-1903-23  
Schwendinger J.  
EP11-197-22  
Schwoebel V. EP23-319-23  
Scott L. OA-16-599-22,  
OA-38-737-24,  
OA-38-741-24  
Scott V. LB-2090-22  
Scourse R. OA-13-577-22,  
OA-15-593-22,  
EP05-147-21  
Scriba T.J. TBS-OA-06  
Seagar A.-L. EP36-451-24  
Seak K. EP18-272-22,  
EP33-425-24  
Seas C. OA-40-745-24,  
OA-40-746-24  
Sebert J. EP20-296-23,  
EP28-366-23  
Sechache L. EP24-329-23  
Seddiq M.K. OA-16-602-22,  
EP21-306-23  
Seddon J.A. OA-02-513-21,  
OA-11-566-22,  
EP02-112-21,  
EP23-324-23  
Seder R. TBS-OA-02  
Seed P.C. EP25-337-23  
Seepamore B.  
OA-06-540-21,  
OA-12-573-22  
Segal L. EP-TBS-33  
Sekaggya-Wiltshire C.  
EP-TBS-61  
Sekandi J. OA-15-597-22,  
OA-26-661-23  
Seldon R. TBS-OA-08  
Self J. OA-25-658-23  
Semianiv I. **EP27-359-23**  
Semira Pasquale M.  
EP18-277-22  
Semitala F. EP36-449-24  
Sen S. OA-35-717-24  
Sen D. EP15-247-22  
Senador L. EP12-211-22  
Seng K. EP19-283-22  
Senin A. EP-TBS-71  
Sentissi I. EP22-313-23  
Sethi P. EP-TBS-39  
Seto S. EP-TBS-08  
Seung K. EP-TBS-80  
Severin L. EP05-151-21  
Severov V. EP-TBS-85  
Sewelana T. OA-02-509-21  
Sgaier S. OA-22-634-23  
Shah A. OA-06-536-21,  
OA-09-553-21,  
EP03-121-21,  
EP14-237-22,  
EP21-298-23,  
EP30-387-24,  
EP33-415-24,  
EP33-416-24,  
EP33-417-24  
Shah M. OA-09-553-21  
Shah I. OA-11-564-22  
Shah T. OA-16-598-22  
Shah T. **OA-16-600-22**  
Shah S.K. EP21-298-23  
Shah J.A. EP-TBS-22  
Shahzad S. EP37-463-24  
Shaik-Dasthagirisahab Y.B.  
OA-03-515-21  
Shaikh A. OA-11-564-22,  
**TBS-OA-05**  
Shaikh M. EP03-122-21  
Shamim A. **EP15-250-22**  
Shanaube K. EP20-290-23  
Shanmugam S.  
OA-34-708-24  
Shapiro A. OA-01-503-21  
Shapiro A.E. OA-05-531-21  
Sharma A. OA-09-553-21,  
EP30-387-24  
Sharma D. OA-21-629-22,  
EP33-417-24  
Sharma S.K. OA-31-690-23  
Sharma B. EP35-438-24  
Sharma R. EP35-439-24,  
EP37-459-24  
Sharma N. EP-TBS-42  
Sharpe S. EP-TBS-13  
Shearer K. **OA-15-594-22**  
Sheen P. OA-05-533-21  
Shen X. OA-32-694-24  
Shenai S. OA-16-600-22  
Shenoi S. LB-2127-24  
Sheremeta Y. EP23-321-23  
Sher-Locketz C.L.  
EP12-210-22  
Sheshi M. EP09-179-21  
Shet A. EP07-162-21  
Shete P. EP13-226-22  
shi I. **EP09-183-21**  
Shi W. TBS-OA-03,  
EP-TBS-18  
Shigut B. EP14-231-22,  
EP14-236-22, EP14-238-22  
Shim E.H. **OA-32-699-24**  
Shim E. EP04-128-21  
Shin J.Y. OA-32-699-24  
Shin J. EP04-128-21  
Shin J.-G. EP-TBS-77,  
EP-TBS-78, EP-TBS-79  
Shingane S. OA-26-662-23  
Shitikov E. **EP-TBS-85**  
Shivakoti R. **EP27-357-23**  
Shongwe M.C. EP33-419-24  
Showket T. EP37-464-24  
Shrestha B. EP02-110-21  
Shrestha S. EP06-157-21  
Shrestha S.K. **EP07-163-21**  
Shuaib N. EP19-286-22,  
EP32-412-24  
Shubladze N. EP-TBS-49  
Shukla P. OA-09-553-21,  
EP03-121-21, **EP30-387-24**  
Shukla S. EP17-263-22  
Shyu C. **OA-05-534-21**  
Siamba S. OA-02-508-21,  
OA-02-510-21,  
EP11-204-22  
Sichone E. OA-18-617-22  
Siddiqui S. OA-34-710-24  
Siddiqui H. OA-37-734-24  
Sidibe K. OA-01-504-21  
Sidney Annerstedt K.  
OA-31-693-23,  
EP04-138-21  
Sidney-Annerstedt K.  
OA-29-682-23  
Sigal G.B. EP-TBS-38  
Silitonga P. **EP04-136-21**  
Silsarma A. EP21-302-23  
Silumesi A. OA-25-657-23,  
EP06-158-21  
Silumesii A. EP21-303-23,  
EP23-323-23, EP30-388-24  
Silva S. **OA-29-680-23**  
Silva A.A. EP-TBS-19  
Silva Rodrigues L.  
EP-TBS-16, EP-TBS-24  
Sim B. EP-TBS-27  
Simeneh A. OA-38-740-24  
Simonsson U.S.H.  
OA-07-543-21  
Simonsson U.S.  
OA-17-607-22  
Simonsson U. EP27-354-23  
Sineke T. EP16-253-22,  
**EP22-315-23**  
Singh U. OA-10-556-22  
Singh S.R. OA-18-614-22  
Singh J. OA-41-753-24  
Singh P. EP01-105-21,  
**EP-TBS-43**  
Singh S. EP31-398-24  
Singh R. EP35-439-24  
Singla N. EP09-184-21,  
EP26-344-23,  
EP26-347-23  
Singla R. **EP09-184-21**  
Sinha P. **EP28-370-23**  
Sinha A. EP29-383-24  
Sinha M.K. **EP35-438-24**  
Sinityn M. EP13-223-22  
Siomak O. EP29-380-24  
Siphanthong P.  
EP28-366-23  
Siroka A. EP05-150-21  
Sitienei J. EP25-335-23  
Sivaramakrishnan G.  
EP-TBS-47  
Siyame E. OA-03-519-21,  
**EP25-342-23**  
Sizaire V. OA-04-524-21  
Sizemore E. EP02-115-21  
Skornyakov S. **EP-TBS-04**,  
**EP-TBS-14**  
Skrahin A. OA-04-528-21,  
EP01-107-21,  
**EP29-383-24**  
Skrahina A. **OA-04-525-21**,  
**OA-04-528-21**,  
**EP01-107-21**,  
EP29-383-24  
Slavchev I. EP34-434-24  
Slim-Saidi L. EP36-450-24  
Sloan D.J. OA-03-517-21,  
OA-25-659-23,  
EP34-429-24  
Sloan D. **EP-TBS-61**  
Sloot R. OA-28-675-23  
Slump E. EP11-198-22,  
EP29-377-24  
Smaoui O. OA-23-645-23  
Smaoui S. EP36-450-24  
Smeijers A. EP10-193-21,  
EP29-381-24  
Smirnova T. OA-11-567-22  
Smit T. EP32-410-24  
Smit Y. EP-TBS-64  
Smith M. TBS-OA-12,  
EP04-129-21,  
EP04-131-21  
Smith J. EP11-206-22,  
EP33-414-24  
Smyth C. OA-12-570-22  
Snyman L. EP17-265-22  
Sohn H. **EP16-251-22**  
Sohn J.H. EP27-360-23  
Sok N. OA-12-570-22,  
EP13-227-22  
Sokoya O. EP37-456-24  
Solanki N.k. OA-06-538-21  
Solans B.P. OA-17-611-22  
Solante M. EP26-351-23  
Sole T.B. OA-01-502-21  
Sole T. **OA-01-505-21**  
Solodovnikova V.  
OA-04-528-21,  
EP01-107-21  
Solon J. OA-18-615-22  
Solon J.A. OA-24-654-23,  
LB-2071-23, EP11-202-22  
Solovieva N. EP29-379-24,  
EP34-434-24  
Somashekar N.  
OA-16-598-22  
Somyala N. OA-12-569-22,  
OA-12-574-22

- Somwe P. EP36-454-24  
 Sonata M.B. EP01-108-21  
 Song R. EP11-206-22  
 Sophonphan J. EP11-201-22  
 Soren P. EP15-247-22, EP37-462-24  
 Sorsavanh T. EP20-296-23  
 Sorum M. OA-10-560-22, OA-19-623-22, OA-36-724-24, EP16-261-22, EP17-268-22, EP37-456-24, EP37-458-24  
 Sossen B. OA-31-688-23, EP03-119-21  
 Sougou N.M. EP07-165-21  
 Souza L.L.L. EP01-101-21, EP36-446-24  
 Souza L. EP19-282-22  
 Souza M. EP19-282-22  
 Souza C.S. EP36-446-24  
 Souza dos Santos M. EP04-137-21  
 Spencer G. OA-33-706-24  
 Spinu V. TBS-OA-04  
 Spire B. EP33-425-24  
 Spitaleri A. TBS-OA-11  
 Squire B. OA-03-521-21, OA-40-744-24, EP16-258-22, EP25-335-23  
 Squire S.B. EP19-278-22  
 Sridhar R. EP01-100-21  
 Srinivasan A. **OA-21-629-22, EP14-237-22, EP33-417-24**  
 Sriplung H. EP21-297-23  
 Sriraman K. **OA-11-564-22, TBS-OA-05**  
 Ssebambulidde K. LB-1968-21  
 S. S. Malaquias T. EP16-259-22  
 S. Soares I.C. EP16-259-22  
 Stagg H.R. OA-04-522-21  
 Stagg H. **LB-2046-24**  
 Stambas J. EP-TBS-29  
 Starke J. OA-31-692-23, OA-38-738-24  
 Stecher M. EP-TBS-07  
 Steenhoff A.P. OA-03-515-21, EP25-337-23  
 Stein M. EP29-381-24  
 Steingart K. OA-41-751-24, EP12-213-22  
 Stella F. OA-17-606-22  
 Sterling T. OA-24-647-23, EP-TBS-82  
 Sterling T.S. EP-TBS-01  
 Stevens W. OA-16-599-22, OA-38-741-24  
 Stevens L. OA-36-725-24, EP26-353-23  
 Stevens R.H. EP34-428-24  
 Stienstra Y. OA-27-668-23  
 Stojanovic Z. EP-TBS-03  
 Stolbrink M. OA-03-520-21, EP25-336-23  
 Strauss M. EP22-308-23  
 Strombu I. OA-35-718-24  
 Strong M. TBS-OA-12  
 Stroup S. EP-TBS-72, EP-TBS-76  
 Struminger B. EP26-344-23, EP26-347-23  
 Strydom N. **TBS-OA-13, EP-TBS-67, EP-TBS-81, EP-TBS-84**  
 Stuber T. OA-34-707-24  
 Sturkenboom M. EP27-363-23  
 Suarez I. TBS-OA-04, **EP-TBS-07**  
 Suarez P. EP06-157-21  
 Suarjana I.K. OA-33-702-24  
 Sudha V. EP01-100-21  
 Sulaiman I. EP-TBS-33  
 Sulis G. OA-10-557-22  
 Sumner T. OA-14-587-22  
 Sun F. EP09-182-21  
 Sun L.P. EP18-272-22  
 Supply P. EP-TBS-53  
 Surtie S. EP-TBS-38  
 Suryavanshi N. EP12-208-22, EP30-386-24  
 Susanto B.O. **OA-07-543-21**  
 Sutar N. OA-26-663-23  
 Suthepmany S. **EP20-296-23, EP28-366-23**  
 Sutherland J. OA-40-743-24, EP22-315-23, EP28-368-23, EP-TBS-11, EP-TBS-12  
 Suzdalnitsky A. EP11-197-22  
 Suzuki S. **OA-24-654-23**  
 Suzuki S.J. **EP11-202-22**  
 Svensson E.M. OA-07-543-21  
 Svensson E. OA-41-752-24  
 Swaleh S. EP08-169-21  
 Swamickan R. OA-06-536-21, OA-09-553-21, OA-21-629-22, EP03-121-21, EP30-387-24, EP33-415-24, EP33-416-24  
 Swe P.P. EP30-391-24  
 Sweeney S. EP16-254-22, EP28-364-23, EP28-365-23, EP28-373-23  
 Switala J. **EP12-218-22**  
 Sy B.A. EP07-165-21  
 Synders C.I. LB-2092-21  
 Székely R. EP-TBS-38  
 Szwarko D. OA-02-511-21
- T**  
 T R. OA-06-536-21  
 Tacheny E. EP-TBS-52  
 Tack I. EP13-228-22, EP20-294-23  
 Tadesse M. **OA-38-740-24**  
 Taguibao C. OA-36-721-24, OA-36-725-24, EP26-353-23  
 Tahir A. EP15-245-22  
 Takeuchi R. **EP-TBS-36**  
 Takwoingi Y. OA-41-751-24, EP12-213-22  
 Tam D.B. EP-TBS-08  
 Tambe M. LB-2115-21  
 Tamirat M. EP11-207-22  
 Tamne S. OA-27-667-23  
 Tan R.K.J. OA-12-570-22  
 Tan Q. **TBS-OA-03, EP-TBS-18**  
 Tan C. EP05-150-21  
 Taneja R. EP-TBS-42  
 Tang Y. EP08-170-21  
 Tanner R. **EP-TBS-13**  
 Tanuri A. LB-2093-22, LB-2100-22  
 Taralekar R. OA-21-626-22, EP09-186-21, EP15-239-22  
 Tarlton D. OA-33-706-24  
 Tartakovsky M. OA-35-718-24, EP-TBS-55  
 Taruvunga T. EP21-299-23  
 Tatum K. EP02-116-21  
 Tauro F. OA-17-605-22  
 Tchabo Fosso A. LB-2047-21  
 Tchounga B. OA-02-508-21, OA-02-510-21  
 Telles H. EP05-145-21  
 Templeton K. EP-TBS-61  
 Teo A.K.J. OA-12-570-22, **OA-18-614-22, EP13-227-22**  
 Terenciani Campoy L. EP04-137-21  
 Terhalle E. TBS-OA-04  
 Terleeva Y. OA-14-591-22, EP29-380-24  
 Terleeva I. OA-21-628-22, EP23-321-23  
 Terray A. EP-TBS-52  
 Thacker D. OA-18-612-22  
 Thai C.H. OA-36-726-24, EP31-399-24  
 Thakur K. EP12-208-22  
 Thakur C. EP37-459-24  
 The AIDS Clinical Trials Group and the Tuberculosis Trials Consortium, EP02-115-21, EP02-116-21  
 Thee S. OA-17-611-22  
 Thein S.T. EP30-391-24  
 Theingi P. **OA-37-728-24**  
 Theron D. OA-32-697-24, EP09-177-21, EP22-318-23  
 Theron G. EP-TBS-33  
 Thi S.S. EP26-351-23, EP30-393-24  
 Thida A. EP09-185-21
- Thior I. **OA-01-500-21, OA-37-730-24**  
 Thomas K. OA-01-503-21  
 Thomas A. OA-16-604-22, EP19-284-22  
 Thomas B. OA-22-634-23  
 Thomas T. OA-37-729-24, LB-2119-21  
 Thomas J. OA-37-733-24  
 Thomas Panwal M. OA-03-516-21  
 Thomaz Mafort T. EP-TBS-16, EP-TBS-24  
 Thomson H. **EP25-336-23**  
 Thuch S. EP33-425-24  
 Thuong P.H. EP-TBS-08  
 Tiam A. OA-02-508-21, OA-02-510-21  
 Ticona E. OA-05-533-21  
 Ticona Chavez E. EP02-110-21  
 Tiemersma E. EP-TBS-64  
 Tiongo M. EP16-262-22  
 Tipre P. OA-26-663-23, EP21-302-23  
 Tobaiwa D.D. **EP21-299-23**  
 Todoriko L. **EP11-200-22, EP27-359-23**  
 Todt K. EP-TBS-50  
 Tolosa G. EP-TBS-03  
 Tomeny E. EP16-258-22, **EP19-278-22**  
 Tomono K. EP-TBS-60  
 Tonby K. LB-2092-21  
 Tonkin-Crine S. OA-12-569-22, OA-12-574-22  
 Tordoya Titichoca I.J. EP14-232-22  
 Toriola M. OA-19-623-22, EP37-458-24  
 Tornheim J.A. **EP-TBS-15**  
 Torres L. LB-2110-24  
 Torres Ortiz A. OA-35-714-24  
 Torres-Puente M. LB-2082-21, EP-TBS-49, EP-TBS-51  
 Toshiwal M.N. EP28-365-23  
 Toumanian S. **EP10-193-21, EP11-198-22, EP29-381-24**  
 Toure N.O. **EP07-165-21**  
 Touw D. EP-TBS-76  
 Tovar M. **LB-2122-22**  
 Trajman A. OA-07-542-21  
 Tran P.T. **EP16-257-22, EP31-396-24**  
 Traore H. EP07-165-21  
 Trappal-Kimmons K. EP-TBS-13  
 Tretiakov V. OA-14-591-22  
 Triccas J. EP-TBS-29  
 Trinona J. EP30-393-24  
 Tripathy S. EP01-100-21  
 Trivino-Duran L. LB-2090-22  
 Trollip A. OA-11-565-22, OA-38-736-24, OA-38-741-24, LB-2110-24

- Truong V.V. OA-28-674-23  
 Tsionsky M. EP-TBS-38  
 Tsuyuguchi K. EP-TBS-60  
 Tsvetkov V. EP-TBS-85  
 Tsvirenko S. EP-TBS-14  
 Tugumisirize D.  
 OA-25-660-23,  
**OA-37-731-24**,  
 EP16-252-22,  
 EP18-274-22,  
**EP36-452-24**  
 Tugumisirize D.T.  
 EP36-445-24  
 Tukur M. **EP19-286-22**  
 Tukvadze N. OA-27-672-23,  
 OA-40-742-24,  
 EP29-378-24  
 Tumblin J.M. EP09-177-21  
 Tumwesigye P.  
 OA-09-550-21,  
 OA-12-571-22  
 Tunggal Mulyandari I.  
 EP20-292-23  
 Tuot S. **OA-12-570-22**,  
 EP13-227-22  
 Turkova A. OA-34-711-24,  
 LB-2056-24, EP02-112-21,  
 EP02-114-21  
 Turner K. **OA-07-546-21**  
 Turner C. EP-TBS-33  
 Turyahabwe S.  
 OA-09-550-21,  
 OA-09-551-21,  
 OA-13-583-22,  
 OA-13-584-22,  
 OA-14-590-22,  
**OA-15-592-22**,  
 OA-37-731-24,  
 LB-2087-24, EP01-106-21,  
 EP04-139-21,  
 EP13-221-22,  
 EP16-252-22,  
 EP18-274-22,  
 EP30-390-24,  
 EP36-452-24  
 Twabi H. **EP03-120-21**  
 Twinomugisha F.  
 EP04-139-21  
 Tyagi J.S. EP-TBS-42  
 Tzelios C. EP14-234-22
- U**  
 U N. **EP30-391-24**  
 Ubochioma E. EP06-152-21,  
 EP08-172-21,  
 EP10-187-21,  
 EP18-273-22  
 Uchimura K. **OA-14-586-22**  
 Ucuncu M. OA-11-567-22  
 Udah D. EP34-433-24  
 Ufimtseva E. EP-TBS-04  
 Ugarte-Gil C. OA-38-735-24  
 Ugube B. OA-36-727-24,  
 EP10-192-21,  
 EP26-348-23,  
 EP32-409-24  
 Uguge I.B. **EP24-333-23**,  
**EP31-403-24**
- Ugwu C. **OA-14-589-22**,  
 OA-14-589-22,  
 OA-23-644-23,  
**EP04-135-21**,  
**EP13-222-22**,  
**EP20-289-23**,  
 EP24-325-23,  
**EP30-392-24**,  
 EP31-402-24,  
 EP32-412-24  
 Ukwaja K.N. EP07-166-21  
 Ullah Khan N. EP08-171-21  
 Ulo B. OA-10-559-22,  
 OA-22-633-23,  
 EP24-326-23,  
 EP26-345-23  
 Umar A. **EP18-276-22**  
 Umar I. EP19-286-22,  
 EP37-458-24  
 Umba P. EP-TBS-54  
 Unnewehr M. TBS-OA-04  
 Upadhyay S. EP37-459-24  
 Upton A. TBS-OA-16  
 Urhioke O. EP12-216-22  
 Useni S. OA-14-588-22,  
**EP09-179-21**, **EP10-187-21**,  
 EP10-192-21,  
 EP11-199-22,  
**EP19-280-22**,  
 EP19-286-22,  
 EP31-394-24,  
 EP31-403-24,  
 EP32-409-24,  
**EP36-447-24**  
 Ushakova N. EP29-379-24  
 Ustero P. **EP05-147-21**,  
**EP12-217-22**  
 Utpatel C. EP-TBS-50,  
 EP-TBS-53  
 Uwaezuoke N.A.  
 EP18-273-22  
 Uwizera A. EP20-295-23
- V**  
 Vaidya D. OA-03-514-21  
 Vaidyanathan D.  
 OA-18-612-22  
 Vakhrusheva D. EP-TBS-04  
 Valcheva V. EP34-434-24  
 Valvi C. EP12-208-22  
 van Aartsen D.  
**OA-37-729-24**,  
**LB-2119-21**, EP-TBS-72  
 van Campen N.  
 OA-25-659-23  
 van Crevel R. TBS-OA-01  
 van Crevel R. EP-TBS-06  
 van de Berg S.  
**OA-27-671-23**,  
 EP05-140-21  
 van den Boogaard J.  
**EP11-198-22**, EP29-377-24  
 van der Grinten E.  
 EP32-411-24  
 van der Heijden Y.  
**OA-24-647-23**  
 van der Heijden Y.F.  
 EP-TBS-01
- van der Laan L.E.  
 OA-17-611-22  
 van der Stuyft P.  
 OA-40-745-24,  
 OA-40-746-24  
 van der Walt M.  
 OA-01-502-21,  
 OA-01-505-21  
 van der Westhuizen H.-M.  
**OA-12-569-22**,  
**OA-12-574-22**,  
 EP26-349-23  
 van der Zalm M.  
 OA-11-566-22  
 van Der Zalm M.  
 EP15-241-22  
 Vandewalle P. EP16-251-22  
 van Dijk J. OA-17-605-22  
 van Dorp L. OA-35-714-24  
 van Ginderdeuren E.  
**OA-28-676-23**,  
**OA-28-677-23**  
 van Heerden J. EP-TBS-38  
 van Helden P. EP-TBS-33  
 van Hest R. OA-27-669-23  
 van Laarhoven A.  
 TBS-OA-01  
 van Leth F. TBS-OA-04  
 van Nispen-Dobrescu R.  
 EP11-198-22  
 Vanqa N. **EP03-125-21**  
 van Rensburg C.  
 EP16-258-22  
 Vanrenterghem A.  
 OA-04-524-21  
 van Rie A. OA-41-752-24  
 van Rie A. OA-28-676-23,  
 OA-28-677-23  
 van Rooyen G.  
 OA-16-604-22  
 van Soolingen D.  
 OA-32-695-24  
 van 't Boveneind-  
 Vrubleuskaya N.  
 EP11-198-22  
 Vanvolsem J. OA-23-645-23  
 van Wyk R. EP21-304-23  
 van Zyl L. EP09-177-21  
 Varella E. EP01-108-21  
 Vargas R. TBS-OA-12,  
 EP-TBS-56, EP-TBS-57  
 Variava E. OA-15-594-22  
 Varizhuk A. EP-TBS-85  
 Vashakidze S. EP-TBS-49  
 Vasiliu A. **OA-41-750-24**  
 Vassall A. EP16-254-22,  
 EP28-364-23, EP28-365-23  
 Vaswani S. TBS-OA-05  
 Vasyliov S. OA-04-527-21  
 Veerasamy M.  
 OA-34-708-24  
 Veesa K.S. **EP07-161-21**  
 Vega V. **OA-40-745-24**,  
**OA-40-746-24**  
 Velen K. OA-36-726-24,  
 EP31-399-24  
 Venkateswaran S.  
 OA-11-567-22,  
**EP19-287-22**
- Verhoef J. EP30-384-24  
 Verma M. LB-2113-22  
 Vernon A. OA-26-665-23,  
 OA-26-666-23  
 Viatushka D. EP01-107-21  
 Vichare P. EP07-161-21  
 victoria L. **EP25-343-23**  
 Victoria A.M. OA-28-679-23  
 Viiklepp P. OA-31-691-23  
 Vijayan S. **OA-26-662-23**,  
**EP03-118-21**,  
 EP37-459-24  
 Vijayaraghavan V.  
 EP-TBS-47  
 Vilaplana C. EP-TBS-49  
 Vilath S. EP28-366-23  
 Vilc V. EP05-151-21  
 Villabito Gabuya R.  
**EP16-262-22**  
 Villamayor L.M.  
 LB-2082-21, EP-TBS-51  
 Villamayor L. EP-TBS-49  
 Villanueva A. EP05-146-21  
 Villar-Hernández R.  
 EP-TBS-03  
 Villarreal-Ramos B.  
 EP-TBS-13  
 Viney K. OA-12-576-22,  
 EP13-225-22,  
 EP28-366-23,  
 EP28-367-23  
 Vinh L. **EP10-190-21**  
 Vinhas S.A. EP03-123-21  
 Vinod Kumar V  
 EP01-100-21  
 Vitko S. EP11-197-22  
 V. Mukamolova G.  
 EP27-354-23  
 Vo L.N.Q. OA-07-547-21,  
 OA-28-674-23,  
 EP10-194-21  
 Vo L.N. EP16-257-22,  
 EP31-396-24  
 von Delft A. EP04-129-21,  
 EP26-349-23  
 Von Delft A. EP04-131-21  
 Vongpanich S. EP28-371-23  
 Vordermeier M. EP-TBS-13  
 Vu V.G. EP25-341-23  
 Vu L. EP28-375-23  
 Vyas A. **EP34-428-24**  
 Vyazovaya A.  
 OA-31-691-23,  
**EP29-379-24**,  
**EP34-434-24**
- W**  
 Waasila Jassat W.  
 EP01-109-21  
 Walakira M. OA-06-537-21  
 Waldman A.L. EP11-197-22  
 Walker A.S. OA-01-503-21  
 Walters E. OA-11-566-22  
 Walzl G. LB-2092-21  
 Waman D. **EP03-122-21**  
 Wambi P. OA-11-565-22,  
 OA-38-736-24,  
**OA-38-738-24**

- Wambua E. OA-19-620-22  
Wan S. EP10-189-21,  
EP27-362-23  
Wandeyi G. **EP31-400-24**  
Wang L. OA-05-535-21  
Wang J.-Y. **OA-07-545-21**,  
OA-07-548-21  
Wang K. OA-09-555-21  
Wang Q. **OA-19-625-22**,  
**TBS-OA-16**, EP-TBS-67  
Wang H. TBS-OA-03,  
EP-TBS-18  
Wang F. TBS-OA-03  
Wang J. LB-1930-23,  
EP08-170-21  
Wang S.-H. **LB-2110-24**  
Wang Y. EP08-170-21  
Wang R. EP25-336-23  
Wang W.-H. EP-TBS-36  
Wangchuk L.Z. EP28-367-23  
Wanyonyi A.  
**OA-22-633-23**,  
EP31-400-24  
Wapamesa C. EP20-290-23  
Warndorff D. OA-34-712-24  
Warner D. TBS-OA-08  
Warren J.L. OA-11-566-22  
Warren R.M. OA-32-697-24,  
EP09-177-21, EP22-318-23  
Warren R. EP01-102-21,  
EP-TBS-33  
Washington R.  
OA-06-536-21,  
EP33-415-24,  
EP33-416-24  
Wasmann R. **OA-41-752-24**  
Watabe S. EP-TBS-36  
Watanabe S. EP-TBS-60  
Watts J. **EP26-349-23**  
W. Dowdy D. OA-24-652-23  
Weber L. **OA-04-524-21**  
Weerasuriya C.K.  
EP06-155-21  
Weerasuriya C.  
**EP28-374-23**, **EP-TBS-34**  
Wei X. **OA-26-664-23**,  
EP05-149-21  
Weil G. LB-2100-22  
Weiner 3rd J. TBS-OA-04  
Weiser J. OA-07-546-21  
Weissman A. OA-36-725-24,  
EP26-353-23  
Wekesa P. OA-19-620-22,  
OA-21-630-22  
Welch S.B. EP02-112-21  
Welu B. OA-05-529-21  
Wenzel R. **OA-03-519-21**,  
EP25-342-23  
Werngren J. EP34-430-24  
Weyenga H. **OA-01-504-21**  
Whalen C. OA-15-597-22  
Whalen C.C. OA-26-661-23  
White J. OA-04-522-21,  
EP13-226-22  
White R.G. OA-14-587-22,  
TBS-OA-07, EP06-155-21,  
EP-TBS-34  
White L. OA-25-658-23,  
EP03-123-21
- White L.F. OA-32-697-24,  
EP09-177-21, EP22-318-23  
White K. EP13-228-22  
White R. EP28-373-23,  
EP28-374-23  
Wickramaarachchi C.M.  
**LB-2051-22**  
Wiesner L. EP09-176-21  
Wijesooriya H. EP35-441-24,  
EP35-442-24  
Wijesuriya H. EP35-443-24,  
EP35-444-24  
Wilkinson R. OA-01-503-21  
Williams B. OA-01-503-21  
Williams M. LB-2110-24  
Wills G. OA-17-610-22  
Wills G.H. **EP02-112-21**  
Wilson D.P.K. OA-05-531-21  
Wilson M.R. LB-1968-21  
Winckler J.L. OA-17-611-22  
Winckler J. OA-41-752-24  
Wingfield T. OA-31-690-23,  
OA-31-693-23  
Winter S. EP-TBS-07  
Winters N. OA-07-542-21  
Wobudeya E.  
OA-11-565-22,  
OA-38-736-24,  
OA-38-738-24,  
**LB-2056-24**,  
**EP02-114-21**, EP12-215-22  
Wolfe A. OA-06-540-21  
Wollenberg K.  
OA-35-718-24, EP-TBS-55  
Wolters B.A. **OA-27-669-23**  
Wong M. EP12-211-22  
Wong E. EP32-410-24  
Wood R. TBS-OA-08  
Wood C.E. EP03-119-21  
Workman J. OA-02-513-21,  
**EP15-241-22**  
Wu S. OA-22-638-23  
Wu S.-H. **OA-35-715-24**  
Wu M.-H. OA-35-715-24  
Wu C. TBS-OA-03  
Wu J. TBS-OA-03,  
EP22-317-23,  
EP34-427-24, EP-TBS-18  
Wu B. EP-TBS-33  
Wurie F. **EP29-382-24**  
Wyen C. EP-TBS-07  
Wyness A. TBS-OA-14,  
EP34-432-24
- X**  
Xia Y. EP08-170-21  
Xiao Y.-X. OA-25-656-23  
Xiao S. EP-TBS-62  
Xie W. TBS-OA-03,  
EP-TBS-18  
Xu Z. OA-09-555-21  
Xu B. OA-29-684-23  
Xu H. LB-2115-21
- Y**  
Yadana S. EP27-357-23  
Yadav V. EP-TBS-43
- Yaesoubi R. EP24-332-23  
Yahyaoui Azami H.  
**OA-34-707-24**  
Yamaguchi A. EP33-424-24  
Yamamura M. EP01-101-21,  
EP04-130-21  
Yamanaka T. **EP28-366-23**  
Yamane A. EP-TBS-60  
Yan H. EP34-427-24  
Yang L. OA-29-684-23  
Yang C. **OA-32-694-24**,  
EP22-316-23  
Yang W. EP10-195-21  
Yang Y. EP10-195-21  
Yaniv Z.R. OA-05-534-21  
Yao X. OA-26-661-23  
Yarmosh D. EP-TBS-52  
Yasi R. EP28-367-23  
Yataco R.M. OA-33-703-24  
Yataco R. EP-TBS-02  
Yatskevich N. EP01-107-21  
Y. Balappanavar A.  
OA-33-704-24  
Yedilbayev A. OA-04-528-21  
Yee A. EP-TBS-13  
Yeldandi V. EP21-302-23  
Yendluri E.B. EP31-395-24  
Yesipenko S. OA-04-526-21  
Yi S. OA-12-570-22,  
OA-18-614-22,  
EP13-227-22  
Yin Z. EP09-182-21  
Yin S. EP33-425-24  
Yoon C. EP36-449-24  
Yoo S. A. EP08-169-21  
You N. LB-1930-23  
Youm E. OA-02-510-21  
Young R.R. OA-03-515-21,  
EP25-337-23  
Yovsyah Y. EP04-136-21  
Yu B. EP10-195-21  
Yu C. EP19-278-22  
Yuan R. EP13-229-22  
Yuen C. EP04-134-21,  
**EP09-180-21**,  
EP14-234-22  
Yuen C.M. EP34-426-24  
Yunita F. **EP01-108-21**
- Z**  
Zadutsa B. EP25-339-23  
Zafari M. OA-16-602-22,  
EP21-306-23  
Zaharieva M. EP34-434-24  
Zaidi A. EP37-463-24  
Zaitseva O. OA-14-591-22,  
**OA-21-628-22**  
Zakari F. EP08-172-21  
Zaki J. OA-01-500-21  
Zalwango S. OA-15-597-22,  
OA-26-661-23  
Zamboni Berra T.  
EP04-137-21  
Zameer M.A. EP17-263-22  
Zar H. OA-41-752-24  
Zawahir S. OA-36-723-24,  
**OA-36-726-24**,  
**EP31-399-24**
- Zawedde Muyanja S.  
OA-12-571-22,  
OA-37-731-24  
Zawedde-Muyanja S.  
OA-13-583-22,  
OA-13-584-22,  
OA-14-590-22,  
OA-15-592-22,  
**EP01-106-21**, **EP13-224-22**,  
EP16-252-22, EP18-274-22  
Zawedde- Muyanja S.  
EP04-139-21  
Zech J.M. **OA-09-552-21**  
Zelnick J. **OA-06-540-21**,  
OA-12-573-22  
Zemsi A. OA-02-508-21,  
OA-02-510-21  
Zeng X. EP04-133-21  
Zenner D. OA-27-668-23,  
EP29-382-24  
Zenteno-Cuevas R.  
EP-TBS-48, EP-TBS-83  
Zephaniah G. EP30-385-24  
Zezai A. EP19-284-22  
Zhang H. OA-29-684-23,  
EP08-170-21  
Zhang Z. OA-33-703-24,  
EP05-149-21, EP-TBS-02  
Zhang N. TBS-OA-16,  
**EP-TBS-67**, EP-TBS-82  
Zhang L. EP04-133-21,  
EP10-189-21, EP27-362-23  
Zhang F. EP04-133-21  
Zhang W. EP09-182-21  
Zhang G. EP09-182-21  
Zhang P. EP09-182-21  
Zhang Y. EP10-189-21  
Zhang X. EP16-260-22,  
EP20-296-23  
Zhao A. **OA-09-555-21**,  
EP13-229-22,  
EP22-317-23, EP34-427-24  
Zhao Q. OA-29-684-23  
Zhao Y. EP04-133-21  
Zhao T. EP08-170-21  
Zhdanova S. EP11-197-22,  
EP-TBS-72  
Zheng X. **OA-29-684-23**,  
EP34-430-24, **EP-TBS-59**  
Zhong L. OA-09-555-21  
Zhou K. LB-2070-24  
Zhou L. LB-2070-24,  
EP10-195-21  
Zhou Z. **EP10-189-21**  
Zhou F. **EP10-195-21**  
Zhou Y. EP22-316-23  
Zhu L. LB-1930-23  
Zhuravlev V. OA-31-691-23,  
EP29-379-24, EP34-434-24  
Zignol M. EP18-271-22  
Ziki P. EP21-305-23  
Zimmer A.J. EP-TBS-38  
Zimmerman E. **EP33-414-24**  
Zindoga P. **OA-28-678-23**,  
**EP28-375-23**  
Zordilla Z. EP28-364-23  
Zulu E. OA-03-521-21  
Zurba L. OA-03-520-21  
Zyambo K. EP23-323-23