Technical Consultation on latent TB infection management: research in support of scale-up

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Montréal, Canada

Meeting Report

Background

Latent tuberculosis infection (LTBI)[1] is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB. It is estimated that about a quarter of the global population has LTBI(1). Among other measures to prevent TB, such as early detection and treatment of active disease and infection control measures, tuberculosis preventive treatment (TPT) constitutes one of the principal interventions recommended by WHO to achieve the targets of the End TB Strategy, as upheld by the UN High Level Meeting on TB held in September 2018(2,3). In 2018, Member States committed to providing TPT to at least 30 million people by 2022: 6 million people living with HIV (PLHIV); four million children <5 years of age who are household contacts (HHC) of TB patients and 20 million other HHCs. Data collected by WHO from Member States suggest that to achieve these targets, global efforts to find and treat people at risk of progression to active TB need to be reinvigorated. In 2018, 65 countries reported initiating TPT for 1.8 million PLHIV, an increase from less than 1 million PLHIV initiated on TPT in 2017 (4). The number of children <5 years reported to have been started on TPT globally in 2018 was close to 350,000, a slight increase from 2017, and about one fourth of estimated children eligible for TPT. For household contacts ≥ 5 years of age, **just over 79 000 people initiated TPT**. This represents a **30% decrease from numbers reported in 2017** (4) and **only about 2% of the estimated number of eligible contacts** targeted by the goals of the UN High Level Meeting in 2018.

Some of the barriers to the worldwide expansion of TPT relate to uncertainties about how best to roll out interventions to find people at risk of LTBI, how to test them and help them start and complete treatment. Recent evidence reviews conducted ahead of updates to WHO LTBI guidelines exposed several knowledge gaps (5) (BOX). These point to the need for research at all *critical* steps of the pathway from development of better diagnostics and treatment to more effective delivery of these products.

BOX: Research priorities in LTBI management (derived from reference 5)

- Risk of progression from LTBI to active TB in different populations
- Potential benefits and harms of testing and TPT in specific risk groups
- Defining the best algorithm for ruling out active TB
- Strategies to save cost and improve feasibility of different approaches to TPT
- Diagnostic tests with improved performance and predictive value for development of active TB
- Shorter, safer, affordable regimens that have a lasting effect regardless of strain and population
- Best strategies to ensure good medication adherence throughout the course of treatment
- Risk of drug resistance following TPT
- Incremental benefit of repeated monitoring of adverse events in different people on TPT
- Cost-effective strategies for LTBI management, including integrated community-based approaches

[1] Given that the main difference from active TB is the absence of disease and infection cannot always be considered latent, the condition is sometimes referred to as TB infection (TBI).

The Global TB Programme of the World Health Organization (WHO/GTB), in partnership with the WHO Collaborating Centre in TB Research at McGill University hosted a meeting in Montréal, Canada, on September 16 2019, to discuss and update the research priorities in LTBI management and implementation. Participants invited included leading researchers in LTBI diagnostics and treatment, representatives of national TB programmes, representatives of governmental and non-governmental initiatives for large-scale implementation of LTBI, other technical agencies, WHO staff and funding agencies. A full list of attendees with affiliations is provided in Annex 1.

Objectives of the Meeting

The specific objectives of the meeting were to:

1. Review the current landscape of research in LTBI, and discuss the most recent advances in diagnosis, treatment, and implementation over the past 5 years;

2. Update and describe the major knowledge gaps and research needs in diagnosis, treatment and implementation of LTBI management in low- and middle-income countries (LMICs); and

3. Identify major barriers in research and implementation of LTBI management in LMIC and formulate an action plan for the most urgent items for governments and donors to invest in.

The major deliverable of the meeting was an action agenda based on the current barriers to LTBI implementation scale up and the corresponding priority research needs, as identified by participants of the meeting. This action agenda is summarized in this report and will also be drafted as a manuscript to be submitted to a scientific journal.

Summary of Presentations

The meeting started with introductions and a brief description of the objectives and background by M. Zignol from WHO. This was followed by a presentation on recent WHO meetings on LTBI implementation research gaps and the rationale for an action agenda by A Matteelli and D Menzies. The presentations that followed were organised around the cascade of care in LTBI management as summarized in Table 1 (adapted from (6)). Research priorities were focused primarily on three at risk populations targeted by the UN in 2018: PLHIV, HHC aged under 5 years, and HHC aged 5 and older.

Table 1: Losses and drop-outs at each step of the cascade of care in LTBI (adapted from (6))

LTBI Cascade step	Proportion with latent TB intended for screening
Step 1: Intended for screening	100%
Step 2: Initially tested for LTBI	71.9%
Step 3: Received a test result	66.7%
Step 4: Referred if test positive	56.0%
Step 5: Completed Medical Evaluation	43.7%
Step 6: Recommended for treatment	35.0%
Step 7: Accepted and started treatment	30.7%
Step 8: Completed Treatment	18.8%

1. Implementation Research- projects and progress

1.1 IMPAACT4TB (G Churchyard, Aurum Institute for Health Research)

IMPAACT4TB (NCT03435146) is funded by Unitaid, with the aim of shaping the market for 3HP; catalyzing scale up of 3HP in 12 high TB burden countries[2] in PLHIV and household contacts < 15 years of age; and evaluating novel models of delivery to support scale up, conduct pharmacokinetic studies, evaluate programmatic implementation in sentinel sites in each of the 12 countries, evaluate cost-effectiveness and model the impact of 3HP scale up in each country and globally. A common protocol was developed to evaluate the programmatic implementation of 3HP in the 12 countries. The objectives are to describe: the feasibility of implementing 3HP among PLHIV and child contacts <15 years of age, treatment limiting adverse events, and the occurrence of TB disease and all-cause mortality. The evaluation will be done at a minimum of 1-2 sentinel sites in each of the 12 IMPAACT4TB project countries, with the aim to enrol 325 PLHIV and all children initiated on 3HP at these sentinel sites.

A second study led by the group is the Choice Architecture for TPT trial, which will evaluate TB preventive therapy prescribing in a cluster-randomized trial nested within the IMPAACT4TB project in Mozambique, Malawi and Zimbabwe. The trial will test a choice architecture that makes prescription of TPT the "default" option: for treatment not to be prescribed, the clinician will need to "opt out" for an individual patient. The primary objective is to test whether choice, compared to standard 3HP implementation, will substantially increase 3HP prescribing. Clinical process data will be used to assess the effectiveness of each strategy by comparing the proportion of PLHIV screened for TB preventive therapy, eligible for 3HP, and prescribed 3HP.

A third nested pragmatic cluster-randomized trial in Ethiopia and South Africa will compare the effectiveness and cost-effectiveness of community-based versus facility-based child contact investigation and TPT initiation among household TB contacts under 15 years of age. The study will compare the ratio of child contacts per pulmonary TB index case who are identified, and who initiate

[2] Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi, Mozambique, South Africa, Tanzania UR, Zimbabwe

and complete TB preventive therapy using either the 3HR or 3HP regimen. This trial will inform the optimal implementation strategy for investigating paediatric household TB contacts.

1.2 CaPTB (M. Casenghi, Elizabeth Glaser Pediatric AIDS Foundation)

Another large scale implementation project is CaPTB. The *Institut de recherche pour le développement* (IRD) will lead the implementation of the CONTACT study (NCT03832023), a cluster randomized study that will assess a community-based intervention for the symptom screening and management of child contacts of pulmonary tuberculosis cases, including household level initiation of the 3-HR regimen. The study will be implemented in Cameroon and Uganda and the intervention will be compared to the existing standard of care in the two countries. The study will compare the proportion of household child TB contacts eligible for TPT (<5 years and HIV-infected children 5-14 years without active TB) who initiate and complete treatment among all identified household child contacts between facility-based and community-based models for contact screening and management in high TB-endemic and resource limited settings.

It is expected that the CaPTB project will also generate evidence through the pre- versus post-intervention analysis that will be performed under the monitoring and evaluation framework implemented for the evaluation of project interventions under routine conditions. It will monitor some critical indicators related to the delivery of TPT along the cascade of care from TB screening to initiation and completion of 3HR in children.

1.3 ACT4 Trial (O. Oxlade, McGill International TB Centre)

The ACT4 trial (NCT02810678) was a multi-centre cluster randomized trial funded by the Canadian Institute of Health Research (7). The aim was to strengthen the management of HHCs of newly diagnosed patients with pulmonary TB, using a three-phase standardized public health approach. Twenty four randomisation units (health facilities or groups of health facilities) were included in 5 countries (Benin, Canada, Ghana, Indonesia and Viet Nam). During the evaluation phase of the trial, a standardized assessment of the current LTBI programme, with a focus on cascade-of-care endpoints, was performed at intervention sites. Standardized open-ended questionnaires on practices, knowledge, attitudes and beliefs regarding TB prevention were also administered to key patient groups and health care workers. At each site, local stake-holders reviewed study findings and selected solutions based on their acceptability, cost and effectiveness. In the strengthening phase of the trial, intervention clinics implemented the selected solutions, along with contact measurement registries and regular in-service LTBI management training. Control sites continued their usual LTBI care with no explicit evaluation, strengthening or training activities. The primary study outcome was the number of HHC initiating LTBI treatment per newly diagnosed active TB patient. Cost effectiveness of the intervention was also evaluated. Overall, the trial was found to be successful with reasonable costs. Study tools that were developed for monitoring and evaluation will be made publicly available.

2. Update on diagnostics for LTBI

2.1 Landscape of latent TB tools- progress and challenges (M Pai, McGill International TB Centre)

Current diagnostic tests for LTBI include tuberculin skin testing (TST) and Interferon Gamma Release Assays (IGRAs). The McGill TB Centre has recently completed an up-to-date review of the annual and cumulative incidence of active TB in persons with a positive TST and/or IGRA in 19 at-risk groups, as well as incidence rate ratios of TB in those with positive versus negative tests in these groups. This review has affirmed the clinical utility of testing in the groups studied.

There are many challenges for countries to adopt and scale up LTBI diagnostics, as summarized below:

Tool	Challenge
Tuberculin	-PPD shortages are reported in many countries, including the US and many European countries. Statens Serum Institut, Denmark, a major tuberculin purified protein derivative (PPD) manufacturer sold their manufacturing unit to a Malaysian owned company in 2017 after several years of supply delays. Private companies (e.g. Span Diagnostics in India) make PPD of unknown quality and some data suggest suboptimal accuracy. India used to manufacture PPD in a public sector company, but stopped production circa 2004 -China has a domestic PPD but little is known about its quality
Newer PPDs	-C-Tb (SSI, Denmark), an improved, more specific RD-1 antigen-based skin test has been validated in trials, but is not commercially available, and has not been endorsed by WHO -Diaskintest by Generium, a Russian company, is commercially available, but with little published evidence, the product is yet to be endorsed by WHO
IGRAs	-While interferon-gamma release assays (IGRAs) like QFT(Qiagen) and T-SPOT.TB (Oxford Immunotec) are included in WHO guidelines & WHO Essential Diagnostics List, these assays are expensive in LMICs. These assays are now being added to the GDF catalogue. -New point of care (POC) IGRAs (e.g. QFT Access and POC ichroma™ IGRA-TB) are yet to be adequately validated or policy-endorsed -In countries like India, Republic of Korea and China, there are locally made IGRAs (e.g. TB Platinum) of unknown quality; these assays are also being misused for active TB diagnosis

Members of the McGill International TB Centre conducted a survey in 2019 of high burden countries to better understand plans and challenges regarding the introduction of new LTBI tests and treatment in HBCs (Manuscript in preparation). Updated results include information from 37 respondents from 24

different HBCs. Respondents included National TB program (NTP) managers or staff members (n=22), staff of NGOs partnered with an NTP (n=5), TB researchers or research center officials (n=4), national TB reference laboratory staff (n=3), health ministry officials (n=1), and physicians (n=2).

Regarding LTBI guideline implementation, only 5 countries reported having LTBI guidelines that are fully implemented (Brazil, Lesotho, Mozambique, Russian Federation and Zambia). Seven countries indicated that their NTP does not have LTBI guidelines (Angola, China, DR Congo, India, Indonesia, Kenya, Myanmar), and the remaining 12 countries reported that LTBI guidelines exist in their NTP, but that these are not fully implemented. Among countries with no LTBI guidelines, the most often cited barrier to guideline development was the prioritization of active TB case finding over LTBI screening (n=5, Angola, China, DR Congo, India, Kenya). Other barriers included financial barriers to program implementation (n=3, Angola, DR Congo, Kenya), and guideline development still being in progress (n=4, India, Indonesia, Kenya, Myanmar). Of the 16 countries using PPD, only 4 reported not having experienced a PPD shortage within the past year, and only 3 (China, Indonesia, Russian Federation) have a local manufacturer of PPD. Six countries reported currently using IGRAs in their NTP, with most citing high cost as a barrier to implementation. Lastly, rifapentine is not available in 8 HBCs, hindering the implementation of the 3HP regimen.

2.2 Digital chest radiography: use and availability and practical challenges (F Khan, McGill International TB Centre)

Ruling out active TB is the first step in LTBI treatment; for this purpose conventional chest radiography (CXR) has a 94% sensitivity rate. Digital X-ray machines have several advantages over analogue as they have lower running costs, are higher quality, emit decreased radiation and allow for distance reading. The main disadvantage however is the high capital cost of purchasing machines.

Not many countries have access to or are using CXR for TB screening and even fewer are using it for HHC screening. Among the barriers to broader use of CXR are costs (given that they are usually paid for by the patient), inadequate access to digital technology and the shortage of qualified personnel for interpretation.

Computer-aided reading (CAR) of CXR for pulmonary TB screening are computer programs that analyze CXR instead of human readers, they produce scores from 0 to 100 or 0 to 1. The higher the score, the higher the likelihood that clinical TB will be present. However, some manufacturers do not provide recommendations about the score to use to distinguish normal from abnormal x-rays. Moreover, little is known about how the score's accuracy varies within and across populations.

There are now 3 commercially available software programs, however the licencing costs are very high. In many studies assessing the accuracy of CAR software for TB screening, the software was applied retrospectively and after pre-training on local CXRs in a manner that is different than how it will be implemented outside of a clinical study. Thus, accuracy reported in screening studies may be overestimated. Some action points on diagnostic accuracy of CXR in LTBI care are: capacity of NTPs to train non-medical staff to interpret CXR, positioning of CAR in screening algorithms (ruling out or increasing pre-test probability for stepwise diagnostic testing), head to head comparison of human reading vs CAR, cost-effectiveness of CAR and CAR for paediatric population. There is much room for

improvement in this area and feedback should be provided to manufacturers of what the ideal CAR should include. WHO will be assessing evidence for different CAD packages applied to TB screening and triage in the course of a Guideline Development Group in June 2020.

Group discussion after this session focused on issues related to limited availability of X-rays - due to high cost of the equipment and need for trained technicians. Given the utility of X-rays for diagnosis of a wide range of health problems, it is evident that X-ray equipment and personnel should not be TB specific. Hence these services could be paid through general health system budgets (including UHC mechanisms), and used for all patients, including TB patients. The utility, and cost-effectiveness of this approach could merit further study.

3. Further research on new regimens for TPT

3.1 Reflections on Treatment of LTBI from the perspective of TBTC (A Vernon, CDC & TBTC consortium)

The US has a long history of treating LTBI. Concerns regarding toxicity due to isoniazid sparked the search for new regimens. A study by Martinson et al, in PLHIV found that 3HP, 3HR, continuous H and 6H all performed similarly and had high completion rates. In Study 26 (NCT00023452) the TBTC evaluated 3HP vs 9H and found that 3HP performed well in HIV-negative adults. Subsequent trial extensions established effectiveness and safety in children aged 2-17 years, and in persons with HIV co-infection. However, 3HP was administered under directly observed therapy (DOT) which was an obstacle to wider implementation. Study 33 (NCT01582711) compared 3HP administered by DOT, self-administration (SAT) or SAT with text message. The US-based subgroup (representing ~75% of the trial population) met a pre-planned non-inferiority threshold of 15% with SAT. Further evidence of high adherence to 3HP was found in a cohort study of 3HP in 3,288 persons from 16 US programs, which also reported an 87% completion rate with DOT. Based on these studies the CDC updated its LTBI treatment guidelines to continue to recommend 3HP, now including children 2-17 years and PLHIV, and with administration by DOT or SAT. Current TBTC engagements with LTBI are focusing on rifapentine based regimens. Study 35 (NCT03730181) is a phase I/II trial of dosage and safety of a novel child-friendly water-dispersible co-formulation of isoniazid and rifapentine in HIV-uninfected and -infected children with LTBI. The purpose is to establish the dose of rifapentine that will achieve in children aged 0-12 years the same exposure as adults in Study 26. TBTC Study 37 (ASTERoiD; NCT03474029) aims to evaluate tolerability and safety of 6 weeks of daily rifapentine 600 mg vs 12-16 weeks of rifamycin-based therapy in high risk population for TB in low TB incidence countries. The group remains open to testing 1HP in Study 37 if a capable partner is identified. CDC continues efforts to optimize targeting of LTBI therapy, as well as to identify shorter safer regimens for TPT.

3.2 1HP updates and future studies (S. Swindells, University of Nebraska Medical Centre)

The 1HP trial (NCT01404312)(8) was carried out in multiple sites among PLHIV aged >12 years. The trial consisted of daily HP (INH 300mg/RPT ~10 mg/kg) for one month compared to nine months of isoniazid, with a follow up period post treatment of 3 years. The incidence rate of TB was very similar among both groups and there was no indication of reinfection over the follow up period. There was a low rate of grade 3 or 4 adverse events, which may indicate that other than a baseline evaluation, 1-HP

could be given without laboratory monitoring. TB incidence rates showed a non-significant interaction with sex, CD4 cell count (lower counts with higher rates) and with a positive IGRA or TST (showing benefit even among those with negative tests). A pharmacokinetic study was also carried out to evaluate drug-drug interactions. No interactions with standard dose efavirenz were reported, but 1HP has not been evaluated with low dose efavirenz. Nevirapine should not be administered with 1HP. Another study is in development to evaluate interactions with 1-HP and dolutegravir. The next steps in the planning stages are to evaluate 1-HP in HIV negative patients, treatment completion and safety of 1-HP vs 3-HP in household contacts, safety and pharmacokinetics trial of 1HP in children, and 1-HP vs 3-HP in pregnant women.

3.3 4R- Updates and Future studies with high dose rifampicin (2R2) (D Menzies, McGill International TB Centre)

Trial evidence from two phase 3 RCTs of the 4R regimen vs. 9H in adults (18 years and over) (NCT00931736) and children (0-17 years) (NCT00170209) were published in 2018, as well as earlier phase 1 and 2 studies coordinated by the same investigators (9-12). Results from the 6012 adults in a phase 3 trial, and 847 adults in an earlier phase 2 trial, indicated non-inferior efficacy for TB prevention, higher completion with 4R, and significantly fewer Grade 3-4 adverse events (AE), or AE resulting in permanent discontinuation of study drug. The phase 3 trial in 829 children indicated superior completion and non-inferior efficacy with no Grade 3-4 AE attributed to study drug in either arm. Secondary analysis in HIV infected persons, as well as persons with other immune deficiency disorders revealed similar findings (manuscript in preparation)

$2R^2$ is an ongoing Phase 2b, partially blind, controlled trial (NCT03988933) which aims to determine if rifampicin taken at double or triple the standard dose for 2 months has better completion rates than the standard dose of rifampicin when taken for 4 months to prevent TB. The regimens will also be compared in terms of their rate of Grade 3 to 5 adverse events. Persons who need treatment for LTBI, will be randomized to three arms in 1:1:1 with rifampicin at the standard dose (10mg/kg/day) for 4 months (control arm); or at double dose (20mg/kg/day) for 2 months (intervention arm 1); or at triple dose (30mg/kg/day) for 2 months (intervention arm 2). The study began in Montreal in August 2019. Participants will be enrolled at 5 other research sites in Canada and Asia (Indonesia and Viet Nam). Participants are followed for 26 months following randomization. The study will end 44 months after the first participant is enrolled. The study is estimated to be fully completed in April 2023.

Drug trials for TB prevention in paediatric populations were not covered in this series of these talks. More details on recently completed and ongoing trials can be found in the TAG Pipeline Report for Pediatric TB diagnosis, Treatment and Prevention, 2019 (page 7-8).
https://www.treatmentactiongroup.org/wp-content/uploads/2011/08/pipeline_tb_pediatrics_2019.pdf

4. Implementation challenges and specific barriers to LTBI expansion

4.1 Access to LTBI diagnostics and drugs (B. Waning, Global Drug Facility)

The Global Drug Facility (GDF) is part of the Stop TB Partnership and is funded by USAID. It is the biggest procurer of TB medication and diagnostic tools, it procures to any country that complies with GDF guidelines. The catalogue of available products is designed to promote rational use of drugs under WHO recommendations for each product.

Among the lessons learned in market shaping, is that consolidation facilitates competition, lower prices and optimized products. One of the longstanding problems in LTBI is the low demand in LMIC for PPD and IGRA. GDF has only been asked to supply these in the last month although there has not been any recent surge in demand. Quantiferon has recently been added to the GDF catalogue. Other new challenges include the creation of new and less expensive diagnostic tests, however, in order to better inform producers, it would be imperative to have an estimate of the demand. Regarding LTBI drugs there is a clear need but modest demand from countries. Many regimens with different formulations fragment the market which in turn affect supply channels and costs. There is an urgent need for the TB community to come to a consensus on which tools to choose to support. Some recommendations include: consolidation of LTBI regimens and formulations, development of pathways to effectively evaluate new LTBI diagnostic tests, plan for strategic new tool deployment and product life cycle management of new and old tools, provide grants to support procurement and technical assistance to expedite new product introduction and finally, pool procurement to negotiate optimal global access prices for new products and advocate for TB funding.

Discussion after the session highlighted the influence that GDF has on drug availability as it commands a significant amount of the global market for TB drugs. It was also mentioned that GDF also now supplies clinical trials with medicines. Difficulties that countries have been having in obtaining and licencing Rifapentine where also discussed. Finally, the Paediatric Anti-tuberculosis Drug Optimization (PADO-TB) initiative was offered as a good example of the TB community working together in decision making in the context of drug development.

4.2 Country Examples of successful LTBI program Scale up

4.2.1 Benin (M Adjobimey, NTP Benin)

Benin has been actively involved in LTBI research studies over the last decade. This includes clinical trials for new preventive regimens and several trials on IPT implementation for child HHC < 5 years of age. Most recently researchers in Benin participated in the ACT4 trial aimed at strengthening the LTBI cascade of HHC of all ages. Through these research studies home visits to improve contact investigation were found to be useful and feasible. LTBI registries were also found to be important to facilitate data collection. Using information gained from these experiences, expansion of TPT to all HIV centres is planned for 2020 (pending financing). Financial barriers remain a major problem for uptake as patients are still required to pay for CXR and TST. Out of pocket travel expenses by patients are also a known barrier.

4.2.2 Viet Nam (Thu Anh Nguyen, Woolcock Institute of Medical Research, Viet Nam)

The ACT4 Trial (see section 1.3) was conducted in 2 provinces in central Viet Nam. Local NTP staff were very engaged throughout the trial in planning and implementation. At intervention sites improvements were seen in the LTBI cascade and the primary study outcome of TPT initiation. Plans for scale up of the intervention to other provinces in Viet Nam are planned over 2019-2023 (pending financial support). Cost calculators have been developed as a tool to plan for financing of scale up, and to negotiate with stakeholders for funding. Health insurance has been identified as a potential reimbursement mechanism for LTBI programs as insurance schemes can pay for many required tests (CXR, health exam, part of TST). Negotiations with Global Fund (GF) to cover costs that are not related to service fees have also been successful. Challenges remain in the procurement of TST.

5. LTBI Financing

5.1 The Economic Transition for Health and Domestic Resource Mobilization – implications for LTBI financing. (A. Pablos-Mendez, Columbia University)

The Golden Era of Global Health saw a 7-fold increase in (vertical) development assistance for health (DAH) which has produced significant gains in TB control and extended overall life expectancy in the world to over 70 years (a grand convergence for equity is under way). In 2018, low and middle-income countries (LMIC) spent US$ 6.9 billion for TB prevention, diagnosis and treatment, and the world invested US$750 million on TB R&D. The Global Plan to End TB estimates that, in LMIC, US$ 12.3 billion will be required in 2020 which translates to a shortfall of US$ 5.4 billion not counting the research and development gap. Where will that money come from?

Changes in the political economy following the financial crisis of 2008-2012 have ushered in a New World Health Era with flat or shrinking DAH. Yet growing economies in what used to be called the "developing world" means local health spending now dwarfs international sources (in the case of TB nearly 90% of spending is domestic, especially in BRICS countries (Brazil, Russia, India and China), though in low-income countries it is only 60%). Except for global public goods like research and development and pooled procurement (e.g. GDF/GF) which should remain a good value for DAH, TB control will be financed through domestic resource mobilization and increasingly as part of reforms for universal health coverage (the subject of this year's UN General Assembly Special Session) - or innovative schemes like market shaping, social impact bonds and International Development Association (IDA) loan leverage. Data are needed on LTBI financing flows, gaps and its coverage under national health insurance schemes.

5.2. LTBI Frontlines First and Financing (T. Evans, McGill School of Population and Global Health)

LTBI should be situated in the context of the vortex of change in health systems that come from both endogenous and exogenous pressures: competing claims on scarce resources (non-communicable diseases, aging population, technological change, expectations), fiscal stagnation (informal workforce), economic shocks and inequalities. The approach to overcoming these pressures should be multifaceted and heading towards a better value for money, within each countries' own budget. Some interlinked

strategies include building a demand for financing, financing global public goods, innovative global market signalling and domestic resources use and mobilization. The first step is advocating that health is a critical dimension of human capital for future prosperity and quality of life and should be protected by universal health coverage. Looking at the case of LTBI the fact that there is a robust pipeline represents huge progress with respect to global public good generation; now manufacturers have to be convinced that there is a market opportunity.

The financing landscape is shifting from donor funded into government funded. Domestic resource use and mobilization in LTBI scale up could increase program efficiency. An example of a useful tool for this purpose is Optima TB, which helps governments achieve maximum impact with the own countries budget allocated to TB. Many reforms may be needed to achieve efficiency, and it depends on the TB community to figure out where they are most needed.

Research Priorities and Action Agenda

Priorities common to all groups (PLHIV, HHC under 5 years, and older HHC), organized by Steps in the Cascade of Preventive TB Care

Step 1- Identification and linkage to care:

There was a clear consensus that linking the 3 population groups to care represented a major challenge and priority for implementation research. Successful models considered were care through other services such as HIV clinics and paediatricians or other child-care providers. However, other models of linkage have been tried in different settings with varying degrees of success. For example, home visits were considered by some participants to be essential to success in identifying and linking persons to care, while others felt that this was an expensive initiative that had little real impact since the greater number of persons identified did not result in greater numbers linked to care and treatment.

Research Priorities: Best mechanisms for linkage to care in these 3 population groups. Specifically, research that evaluated best practices and alternative methods to enhance linkage to care provided by HIV services, child care services and family health or primary care services. Future research could use modelling studies to better characterise the impact of different strategies in different contexts. Qualitative research could also be helpful to identify acceptability and feasibility issues of different treatments and models of care.

Step 2- Initial evaluation (LTBI testing):

There was broad consensus on the need for a test that would identify individuals at highest risk of progression to active disease, in populations traditionally considered at risk for TB exposure, infection and disease. A more predictive test would allow more streamlined evaluations and treatment of fewer persons, hence allowing programmes to focus resources on a smaller number of individuals. However, some viewed this as too aspirational, given little indication from basic science research that suggests a candidate test in the foreseeable future. Hence the development of a better predictive test is at least 5 or even 10 years in the future. In the meantime, there was also consensus that access to current LTBI tests is very limited and a major barrier to use of LTBI testing and treatment at large scale. Meeting participants viewed the IGRAs as having too many infrastructural requirements and being too costly

(unit test costs as well as need for laboratory infrastructure and laboratory personnel) for routine programmatic use in most LMICs. On the other hand, the TST, using traditional PPD, was almost impossible to access due to limited production globally, much of which may not be of established quality.

Priorities for research: In the immediate and short-term, the need to re-evaluate LTBI testing using currently available tests was judged low among children under age 5, and high among household contacts aged 5 and older. Among PLHIV, the wealth of studies from sub-Saharan Africa were noted, particularly in PLHIV not receiving ART. It was suggested that an assessment of the benefit of LTBI tests in PLHIV on ART and/or in settings with lower rates of TB incidence and transmission could be useful. A second priority was the urgent evaluation of new, more specific TSTs, and point of care (POC) IGRA tests (when they become available); these may prove to be feasible, robust and cost-effective alternatives to currently available IGRAs. The evaluation of these new LTBI tests should include sensitivity, specificity, predictive ability, as well as operational cost and feasibility in primary care settings. In the longer term: continued fundamental research in the mechanisms of latency to identify candidate tests to identify those at highest risk of development of active TB.

Step 3- Medical evaluation to exclude active TB and recommend TPT:

The problems of costs as well as limited access to tests to accurately exclude active TB in the three population groups were noted. Current reliance on CXR is problematic due to outdated technology in many settings, limited access to radiography machines and skilled interpretation of the chest radiographs, and high unit costs for each CXR. In addition, radiography is associated with direct and/or indirect costs to patients in most instances, whether radiography forms part of the TB diagnostic algorithm or not. As patients end up paying out of pocket, this creates a major barrier.

Research Priorities: Immediate or short-term: Development and testing of software for computerized interpretation of digital CXR, especially in specific risk groups (ie. paediatrics). Cost-effectiveness and feasibility evaluations of expansion of digital radiography in primary care settings in low- and middle-income countries. Longer term: Development and assessment of alternative methods to exclude active TB and identify individuals in whom latent TB therapy is safe (primarily to minimize the risk of acquired drug resistance by inadvertent treatment of unrecognized active TB). Health systems research to evaluate the utility and cost-effectiveness of expanded X-ray access through provision of these facilities to all patients, and payment through general health services would also be useful.

Step 4- TPT:

The past 20 years have seen substantial progress in developing, testing and rolling out shorter rifamycin-based regimens ranging in duration from 1 to 4 months. There was clear consensus on the value of shorter regimens that are also very safe. Barriers to treatment include the known risks of isoniazid-based therapy, particularly for adults, the lengthy duration plus need for close follow-up given the possibility of adverse events, and providers' concerns about adverse events and generation of drug resistance by TPT. Additional barriers include skepticism about the benefit of TPT, impression that TB is difficult to rule out, costs and resource limitations for patients and providers related to contact investigation, stockouts of commonly used drugs for TPT.

Research Priorities: Short-term: Evaluation of regimens of 1 to 2 months duration for efficacy, safety, tolerability and acceptability in all 3 population groups. Secondly, to explore patient and provider attitudes to TPT and ways to overcome these barriers to acceptance of treatment. Research on the most effective way to accurately monitor and track adverse events related all TPT regimens in programmatic settings is also needed. Safety of all TPT regimens in pregnant and breastfeeding women also needs further evaluation. Long term: Shorter regimens and/or long acting single dose regimens (for example 'depot' injections of a long-acting agent).

Financing of latent TB care:

The issue of financing LTBI care and the advantages of alternate funding mechanisms, particularly as countries are moving towards adopting universal healthcare systems were noted. Such initiatives, together with rapidly expanding resources for health care in many countries, offer an opportunity to expand LTBI care through coverage of services by general health programmes including primary care providers, rather than TB programmes. This would be feasible if LTBI diagnosis (including exclusion of active TB) is simple, and TPT is very safe.

Research priority: Develop and test models of latent TB care delivery in different countries with different models of care provision and payment. Feasibility, safety, acceptability by patients and providers, as well as net health system costs and patient costs should be evaluated.

Patient Voice:

Finally, research priorities, particularly those with limited consensus by researchers and providers, need to be informed by careful consultation with patients. Issues such as acceptability of testing, use of different algorithms of different complexity for investigation, the trade-offs of convenience, duration and safety of treatment, should be considered by patients and patient representatives. Understanding patient perspectives on risk vs benefit is another area for exploration.

Research priorities specific to the 3 population groups

PLHIV:

It is recognized that PLHIV who are LTBI test-negative still have an important risk of developing TB. However, there is weak evidence that TPT is of benefit for PLHIV who have negative LTBI tests. With recent massive changes in availability, acceptance and efficacy of ART, as well as changing epidemiology of TB and HIV, it is likely that the groups who may benefit from TPT will change. This is particularly true given the advent of shorter, and safer rifamycin based TPT regimens. Hence research will be needed to re-evaluate the benefits and risks of TPT with or without LTBI testing in PLHIV of different ages and in diverse epidemiologic settings. In addition, PK studies of new TPT regimens were recommended, as well as further evaluation of safety and drug-drug interactions for those on ART. Safety in pregnant women is also a specific concern based on the recent P1078 TB Appris trial results

HHC under 5 years:

Areas of research to prioritize included: access to care (particularly overcoming barriers such as stigma and beliefs of parents), best methods to rule out active TB, in view of the well-known difficulties of CXR and symptom screen interpretation in young children. Child-friendly formulations for TPT, particularly HP combinations. Safety and tolerability of the currently available HP shorter regimens drug-drug interactions between these regimens and pediatric ART or malaria medications require further research.

HHC aged 5 years and more:

This is by far the largest group of persons considered high priority for TPT in all settings. Given the discouragingly low rates of TPT initiation for this group globally (4), it is not surprising there were many research priorities for this group. These included the advantages and disadvantages, from individual and public health perspectives, of LTBI testing using current or new tools, the epidemiologic impact of treating household contacts of varying age ranges, the public health benefits in terms of active case finding, questions related to linkage to care and models of care for community delivery of TPT, including digital adherence technology to manage the cascade in the community (including testing) and to support treatment by SAT. A final priority was the development and assessment of more efficient and effective diagnostic algorithms to rule out active TB. Access to care is a major question; household contacts may be identified as a result of active case-finding efforts around an index case of active TB in the household. Hence, they are known to the TB programme, but can TB programmes handle the additional load of investigation and treatment of all the HHCs for active or latent TB on top of their standard work? Hence a high priority must be given to investigate and evaluate alternative mechanisms, such as involving primary care providers or community health workers, for the management of LTBI in HHCs. This would entail a major shift in TB programmes from direct care to setting standards, training, monitoring and quality control of LTBI care. In most high-income countries, National TB programmes made this switch years ago, often because they had little alternative.

Meeting conclusion and way forward:

Over the past two decades, a great deal has been accomplished, most notably in the development and testing of shorter and safer latent TB therapy, and in provision of a full package of LTBI care to HIV-infected populations (often through HIV programs). However, much remains to be done, especially for those receiving care through TB programs that are currently over-whelmed.

In line with the deliverables outlined at the beginning of this report, meeting attendees provided comments on a draft of this report ahead of its finalization. A manuscript is being prepared to summarise the action agenda based on the current barriers to LTBI implementation scale up and the corresponding priority research needs, as identified by participants of the meeting. A draft of the manuscript will be prepared in early February 2020 and will be finalized and submitted for publication in April 2020. As a follow-up to this meeting, WHO will work with partners to update the LTBI research agenda in 2020.

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Glossary of acronyms and other abbreviations

1-HP	1 month of daily isoniazid and rifapentine
3-HP	3 months of weekly isoniazid and rifapentine
3-HR	3 months of daily isoniazid and rifampicin
4-R	4 months of daily rifampicin
6-H	6 months of daily isoniazid
9-H	9 months of daily isoniazid
AE	adverse events
BMGF	Bill and Melinda Gates Foundation (US)
BRICS	Brazil, Russian Federation, India, China and S Africa
CAR	computer aided reading
CXR	chest radiography (X-ray)
DAH	development assistance for health
DOT	directly observed treatment
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation (Switzerland)
GDF	Global Drug Facility (Switzerland)
GF	Global Fund to Fight AIDS, TB and Malaria
HHC	household contact
HIV	human immunodeficiency virus
IGRA	interferon gamma release assays
IRD	Institut de recherche pour le développement (France)
LTBI	latent tuberculosis infection
LMIC	low- and middle-income countries
NTP	national tuberculosis control programme
PLHIV	people living with HIV
POC	point of care
PPD	purified protein derivative
RCT	randomised controlled trial
SAT	self-administered treatment
SSI	Statens Serum Institut (Denmark)
TB	tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases (Switzerland)
TPT	tuberculosis preventive treatment
TST	tuberculin skin test

Annex 1: list of participants

1.	Zignol, Matteo	WHO/GTB, Switzerland
2.	Falzon, Dennis	WHO/GTB, Switzerland
3.	Kanchar, Avinash	WHO/GTB, Switzerland
4.	Menzies, Dick	McGill University, Canada
5.	Oxlade, Olivia	McGill International TB Centre, Canada
6.	Schwartzman, Kevin	McGill University, Canada
7.	Campbell, Jonathon	McGill University, Canada
8.	Pai, Madhukar	McGill University, Canada
9.	Ahmed Khan, Faiz	McGill University, Canada
10.	Evans, Timothy	McGill University, Canada
11.	Chaisson, Richard	Johns Hopkins University, USA
12.	Swindells, Susan	University of Nebraska Medical Centre, US
13.	Salazar-Austin, Nicole	Johns Hopkins University, US
14.	Churchyard, Gavin	Aurum Institute for Health Research, South Africa
15.	Nahid, Payam	University of California San Francisco, US
16.	Cirillo, Daniela	Supranational TB reference Laboratory, Italy
17.	Trajman, Anete	Rio de Janeiro State University, Brazil
18.	Waning, Branda	Global Drug Facility, Switzerland
19.	Brigden, Grania	UNION, Switzerland
20.	Hill, Jeremy	KNCV, The Netherlands
21.	Achar, Jay	MSF, UK
22.	Távora dos Santos Filho, Ezio	Civil Society Task Force, Brazil
23.	Nguyen, Thu Anh	Woolcock Institute, Viet Nam
24.	Adjobimey, Menonli	National TB Programme, Benin
25.	Go, Unyeong	National TB Programme, Republic of Korea
26.	Casenghi, Martina	Elizabeth Glaser Pediatric AIDS Foundation, Switzerland
27.	Lienhardt, Christian	Institut de recherche pour le développement, France
28.	Penazzato, Martina	WHO/HIV, Switzerland
29.	Merle, Corinne	Special Programme for Research and Training in Tropical Diseases (TDR), Switzerland
30.	Ruhwald, Morten	FIND, Switzerland
31.	Bansbach, Cathy	Bill and Melinda Gates Foundation, US
32.	Ahmedov, Sevim	USAID, US
33.	Barreira Cravo Neto, Draurio	UNITAID, Switzerland
34.	Garcia Edward, Celeste	GFATM, Switzerland
35.	Coggin, William	CDC, US
36.	Matteelli, Alberto	University of Brescia, Italy
37.	Vernon, Andrew	CDC, US
38.	Al-Samarrai, Teeb	Office of the Global AIDS Coordinator, US
39.	Mendez, Ariel Pablos	Columbia University, US
40.	Nambiar, Sumathi	FDA, US
41.	Cieren-Puiseux, Isabelle	Sanofi, France

Annex 2: meeting agenda

8:30-9:00	Registration and introductions	
9:00-9:15	Welcome and meeting objectives	Matteo Zignol
9:15-9:30	Past WHO meetings on LTBI implementation: research gaps and an action agenda	Alberto Matteelli & Dick Menzies
Implementation research – projects, applications and progress		
9:30-9:50	IMPAACT4TB /3HP - Experience and update on scale up	Gavin Churchyard
9:50-10:10	Delivery of TB Preventive Treatment to children: CaP TB countries preparedness and early experiences	Martina Casenghi
10:10-10:40	ACT4 - Results, plans for scale up	Olivia Oxlade
10:40-11:10	**BREAK**	
11:10-11:40	Landscape of latent TB tools - progress and challenges	Madhukar Pai
11:40-12:00	Digital CXR: use and availability and practical challenges	Faiz A Khan
12:00-13:00	**LUNCH**	
Further research on new LTBI treatment		
13:00-13:20	3HP and 1.5P – TBTC ongoing and planned LTBI studies	Andrew Vernon
13:20-13:40	1HP- Updates and future studies	Susan Swindells
13:40-14:00	4R – updates and future studies with high dose Rif ($2R^2$)	Dick Menzies
Implementation challenges and specific barriers to LTBI expansion		
14:00-14:25	Access to LTBI diagnostics and drugs: old problems and new challenges	Brenda Waning
14:25-14:50	Country examples of successful LTBI programme scale up	Mênonli Adjobimey (Benin) Thu Anh Nguyen (Viet Nam)
14:50-15:20	**BREAK**	
Implementation challenges and specific barriers to LTBI expansion		
15:20-15:45	The Economic Transition for Health and Domestic Resource Mobilization	Ariel Pablos-Mendez
15:45-16:10	LTBI, Frontlines First and Financing	Timothy Evans
16:10-16:45	Where do implementation research and programmatic management of LTBI treatment fit in the donor agenda?	BMGF; Global Fund; UNITAID; USAID
Discussion and Next Steps (30 mins each session)		
16:45-17:15	Action items - Group discussion to finalize and prioritize. Identification of who will do what	Dick Menzies & Dennis Falzon
17:15-17:30	Closure and thanks	Dennis Falzon

Annex 3: Declarations of Interest of meeting participants

The following participants declared no interests that could conflict with the objectives of the meeting:

Menonli Adjobimey, Grania Brigden, Jonathon Campbell, William Coggin, Celeste Garcia Edwards, Timothy Evans, Unyeong Go, Jeremy Hill, Christian Lienhardt, Alberto Matteelli, Richard (Dick) Menzies, Sumathi Nambiar, Olivia Oxlade, Nicole Salazar-Austin, Kevin Schwartzman, Susan Swindells, Anete Trajman, Brenda Waning.

The following participants declared interests that may be relevant to the objectives of the meeting:
Jay Achar declared that his employer, MSF, has an interest in various aspects of global policy influencing TB control and receives external funding from UNITAID, the Dutch National Lottery and other sources for the implementation of the endTB project and the TBPRACTECAL clinical trial.

Faiz Ahmad Khan declared that he is co-investigator in a 2-month LTBI trial of high-dose vs. normal dose rifampicin supported by the Canadian Institute of Health Research (CIHR). He is also principal investigator in a study to assess accuracy of artificial intelligence program for computer-aided diagnosis of TB in digital chest radiography (CA$487k operating costs from CIHR). No funding provided by developers or companies of software being evaluated. Delft (CAD4TB) & QURE.AI provide technical assistance with using their software, and QURE.AI provided access to their software free of charge for evaluation; the companies have no influence or input on study design & reporting. He was also a member of a WHO steering committee for a consultation on the use of CXR in TB diagnosis.

Martina Casenghi is in the project management leadership for the CaP TB project, funded by UNITAID. This project includes an operational research study on models of care for delivery of TB preventive treatment to child contacts. The study will use the 3RH regimen. The study is led by *Institut pour la Recherche et le Développement* (IRD) and she is a co-investigator. As a representative of one of the stakeholders supporting the roll-out of TPT in endemic countries, she has been invited to stakeholders' meetings and consultations. Her contributions have been aimed at ensuring the specific needs of the pediatric population are taken in consideration by donors and public health organizations.

Dick Chaisson benefited from direct and institutional (Johns Hopkins University; JHU) funding in recent years. This includes a total of about US$2.6 million for research grants from NIH, US CDC, Chao Foundation, UNITAID and Aurum Institute; US$5000 from Sanofi for technical consulting (JHU); and about US$5000 for speaking honoraria from NIH, US CDC, Stop-TB Japan, Portuguese Infectious Disease Society and several US universities.,

Gavin Churchyard declared ongoing research support from UNITAID, USAID, NIH, and Sanofi. UNITAID provided a grant of US$59 million for scaling up of 3HP and implementation research. USAID provided a grant of US$14.2 million to evaluate 3HP given once or annually. NIH provided minimal salary support for the PHOENIx trial. Sanofi donated 3HP for the WHIP3TB trial.

Daniela Cirillo declared that the Supranational TB Laboratory in Milan where she works is developing new diagnostics for drug-resistant TB. She declares current research support from FIND (US$26,000); participation in a national expert group to establish use of bedaquiline in Italy (EUR1000; 2014); support to the standardization of the DST methods for bedaquiline by Janssen (US$10,000; 2014); support to the DST methods for delamanid from Otsuka (US$25,000; 2014). The Ospedale San Raffaele to which the laboratory belongs has a service agreement with the TB Alliance (US$19,800).

Payam Nahid declares an active federal US CDC contract to support clinical trial units in San Francisco and Hanoi, Viet Nam.

Thu Anh Nguyen works fulltime in Viet Nam for the Woolcock Institute of Medical Research, an Australian non-profit organization. Operational research on LTBI using funding from Australia National Health and Medical Research Council

Madhukar Pai serves as the Chair of the Stop TB Partnership's Public Private Mix Working Group; the Access Advisory Committee of TB Alliance (New York); the Scientific Advisory Committee of FIND, Geneva; SAGE IVD and STAG TB Committees of WHO, Geneva.

Morten Ruhwald declared he works for FIND which collaborates with industry (e.g. Cepheid, Hain, Alere, Roche and others) to drive the development, evaluation and distribution of novel diagnostics. No income is received or will be received from these companies. Industry partnerships are approved and monitored by an independent scientific advisory committee based on due diligence and their ability to meet TPPs and public sector requirements. FIND has not allocated any financial value to the know-how or access to equipment gained by these projects.

Ezio Távora dos Santos Filho declared delivering a talk at the Regional IAS Conference in April 2018 in Mexico City on the need for advanced tools for LTBI treatment, without endorsing any particular study. He also declared that as TB advocate he participated in many discussions with the Global TB Community Advisory Board and the Brazilian National TB CAB on the implementation of new LTBI treatment methods. The Brazilian TB CAB is now raising awareness of 3HP and LTBI.

Andrew Vernon declares that he heads a clinical research group at US CDC (TBTC) doing TB trials. TBTC has conducted studies on LTBI and has studies underway with rifapentine (e.g. TBTC Study 31). Over the past two decades TBTC accepted support from commercial and pharmaceutical companies in the form of drug supplies and funding for PK testing. Most recently TBTC collaborated with NIH and Sanofi to undertake the daily rifapentine Phase 3 multi-centre trial. Sanofi provided medicines and funded PK testing but was not involved in the design or conduct of the study. In 2007-2017 Sanofi Aventis made contributions to CDC Foundation (about US$3 million total) to facilitate or support TBTC work on rifapentine (e.g. PK studies, 2-3 staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited Dr Vernon or the research group; these funds represent a small proportion of overall costs for the studies. In his capacity as a TB researcher and clinician at US CDC he has participated in meetings, both internal and external, concerned with the development of guidelines for the treatment of active and latent TB in the US; this has only been within the context of CDC employment and never on behalf of any commercial or non-governmental organization.

Exempted:

funding agencies: Sevim Ahmedov, Teeb Al-Samarrai, Cathy Bansbach, Draurio Barreira Cravo Neto, Celeste Garcia Edward

drug manufacturer: Isabelle Cieren-Puiseux