

TB preventive treatment in high- and intermediate-incidence countries: research needs for scale-up

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SUMMARY

BACKGROUND: In 2018, the WHO Member States committed to providing TB preventive treatment (TPT) to at least 30 million people by 2022. However, only 6.3 million people had initiated TPT by the end of 2019. Major knowledge gaps and research needs in diagnosis, treatment and the programmatic management of TPT (PMTPT) require to be addressed urgently.

METHODS: In September 2019, a group of stakeholders involved in PMTPT in high TB burden countries met to develop an action agenda to support the global expansion of PMTPT.

RESULTS: Barriers at the health system level, and priorities for research to overcome these, were identified

for each step of the PMTPT cascade. The need for data on TPT financing, gaps and coverage under national health insurance schemes, as well as the need for mathematical and cost-effectiveness modelling of the impact of TPT on TB incidence and mortality were highlighted. Specific research needs were identified for high-risk populations such as household contacts of any age and people living with HIV, as well as other people at risk.

CONCLUSIONS: The meeting facilitated agreement on a set of actions needed to ensure that PMTPT continues to expand to achieve the End TB Strategy targets.

KEY WORDS: End TB Strategy; diagnosis; treatment

TB infection (TBI), previously referred to as latent TB infection, is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of TB disease.¹ It is estimated that about a quarter of the global population has been infected with *M. tuberculosis*.² By preventing incident TB cases, TB preventive treatment (TPT) constitutes one of the principal interventions recommended by the WHO to achieve the targets of the End TB Strategy.³ TPT fits within a larger framework of preventive actions envisaged by Pillars 1 and 2 of the End TB Strategy, ranging from screening for TB disease, infection control, prevention and care of HIV and other comorbidities and health risks, access to universal health care, social protection and poverty alleviation. At the UN High-Level Meeting (UNHLM) on TB in 2018,⁴ Member States committed to providing TPT to at least 30 million people by 2022, including 6 million people living with HIV (PLHIV), 4 million household contacts aged <5 years and 20 million household contacts aged ≥5 years.

The WHO issued guidelines for the programmatic management of TB preventive treatment (PMTPT)⁵ that provide recommendations on the implementa-

tion of PMTPT, including selection of target populations, diagnostic and treatment standards, as well as tools for implementation and monitoring and evaluation.⁶ However, the number of people provided with TPT has increased very slowly in recent years, from 1.0 million in 2015 to 2.2 million in 2018 and 4.1 million in 2019. The combined total of 6.3 million by the end of 2019 was only 21% of the UNHLM 5-year target of 30 million.⁷ In 2019, 433,156 recipients of TPT were children under 5 and only 105,240 household contacts ≥5 years. The remaining 3.5 million who initiated TPT were PLHIV.⁷ There are many reasons for the slow uptake of TPT in high and intermediate incidence countries. A recently published global survey identified fragmented implementation of global TPT guidelines and limited access to necessary diagnostic tools as major barriers.⁸ Studies from several countries in Asia have reported current challenges with PMTPT, and described many issues related to diagnosis and treatment.^{9,10}

Here, we report the results of an expert consensus meeting convened by the WHO and the McGill International TB Centre, McGill University, Montreal, QC, Canada. Full details of the agenda,

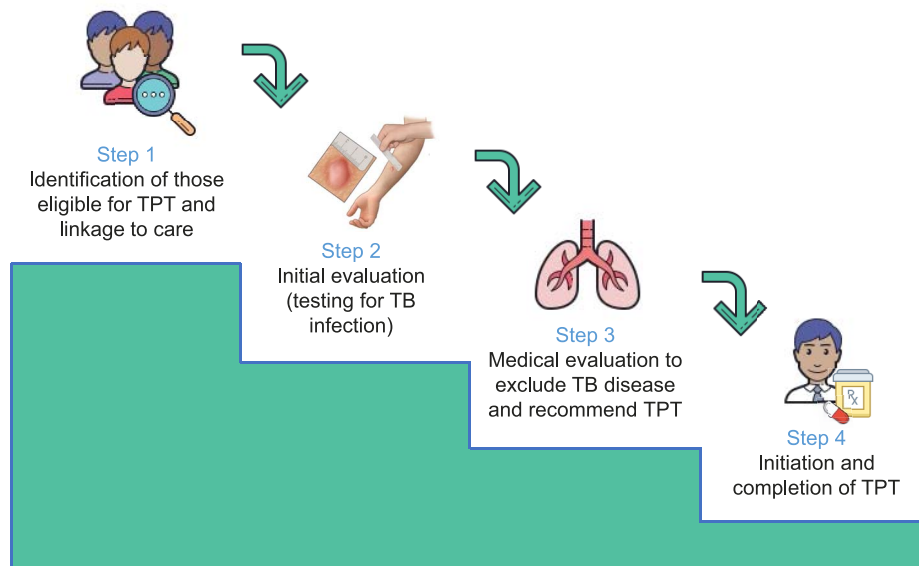


Figure 1 Cascade of prevention for the programmatic management of TB infection. TPT = TB preventive treatment.

presentations, findings and attendees can be found in the official meeting report.¹¹

METHODS

In September 2019, a meeting was convened by the WHO and the McGill TB Centre to discuss the major knowledge gaps and research needs to support the roll out of PMTPT in high and intermediate incidence countries. The meeting also aimed to formulate recommendations for the most urgent action items for governments and donors. Stakeholders from major funding agencies, international organisations, national TB programmes (NTPs) and academic institutions involved in TB prevention were invited. Industry representatives were also invited to provide input from the manufacturing perspective. All attendees completed conflict of interest forms as per WHO protocol. Full details of participants are provided in the appendix. Ethical approval was not required for this activity.

The discussion was structured around the cascade of care in the management of TBI, defined as a multi-step process of individuals moving through the health system, to receive care for TBI.¹² For each step of a four-step cascade model (Figure 1), the participants identified known barriers, knowledge gaps and future research needs. The discussion focused on three at-risk populations: PLHIV, household contacts of TB patients aged <5 years and household contacts aged ≥5 years, as these were the three risk groups specifically identified in the UN General Assembly Declaration.⁷ Other people at risk were considered briefly. During the workshop draft recommendations were crafted, and finalised through multiple revisions until final consensus was achieved among all work-

shop participants who did not have identified conflicts of interest.

Implementation barriers and research gaps for TPT expansion

We first identified general barriers to TPT expansion, including the lack of priority for national TB programmes and the lack of awareness among healthcare workers, as well as barriers to access to diagnostics and preventive treatment, challenges with financing and understanding the perspective of the person who is infected with *M. tuberculosis* (Table 1 and Figure 2). We then identified barriers and research gaps related to specific steps of the TPT care cascade. Issues that relate specifically to PLHIV, household contacts under 5 years, household contacts over 5 years, and other people at risk are described in detail in the following section.

Lack of priority Barriers

For decades, PMTPT has been a low priority for NTPs due to limited funding and other competing priorities. Another important barrier to the implementation of PMTPT is the lack of priority among healthcare workers, and lack of awareness of WHO and/or national recommendations on PMTPT. Health workers may also be hesitant to implement PMTPT because of the fear of development of drug resistance or other adverse events from treatment in otherwise healthy individuals.⁹

Research gaps

Modelling studies have shown that PMTPT can significantly contribute to reducing TB incidence at the population level,¹³ but further mathematical

Table 1 General barriers and research gaps

General barriers	Research gaps
Lack of priority	<ul style="list-style-type: none"> Evidence to build a stronger argument for the case of PMTPT to lower TB incidence and mortality to the levels envisaged by the End TB Strategy targets Estimate (from mathematical modelling) at which scale of PMTPT we would see an impact on incidence and mortality at the population level Address questions about whether we have the tools to roll out PMTPT and what additional tools would support implementation and scale-up of TPT
Access to diagnostics and drugs	<ul style="list-style-type: none"> Consolidate regimens and formulations for TPT Improve procurement and life cycle management of new and old tools Invest in financial tools to support procurement and technical assistance to expedite new product introduction
Financing	<ul style="list-style-type: none"> Improve understanding of financing, gaps and coverage under national health insurance schemes Testing of novel approaches of TPT care delivery in countries with different models of care provision and payment
Understanding the patient perspective	<ul style="list-style-type: none"> Acceptability of testing, use of algorithms of different complexity for investigation, the trade-offs of convenience, duration and safety of treatment Understanding patient and provider perspectives on risk versus benefit of TPT

PMTPT = programmatic management of TPT; TPT = TB preventive therapy.

modelling is needed to show the impact of potential contribution of PMTPT to reducing TB incidence and mortality in different epidemiological situations. Such research should demonstrate the population benefits of PMTPT in reducing the global TB burden for NTPs, implementers, and donors, and the individual benefits of TPT for healthcare workers. Mathematical modelling can also address questions about which tools (e.g., diagnostics, treatment) would have the greatest impact, at what cost, and

what additional tools would support implementation and scale-up of PMTPT.

Access to diagnostics and treatment

Barriers

The tuberculin skin test (TST) based on purified protein derivative (PPD), and interferon-gamma release assays (IGRAs) are currently used to diagnose TBI. Although TST has lower specificity for infection in areas with high bacilli Calmette-Guérin (BCG)

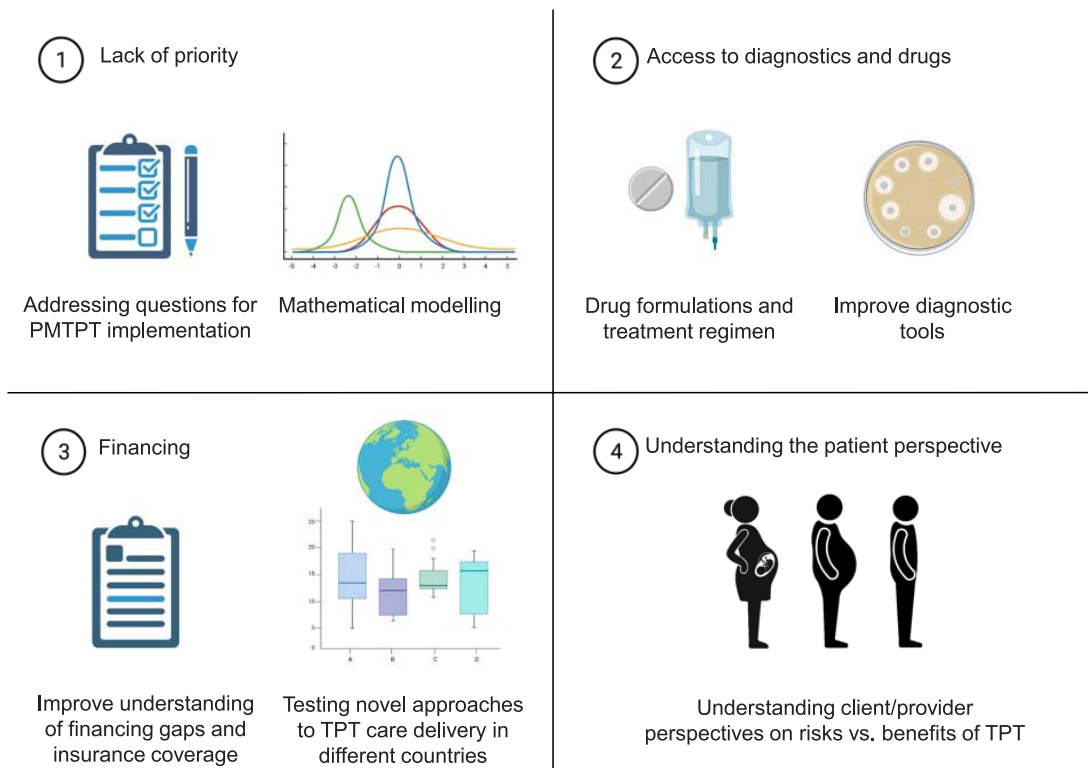


Figure 2 Barriers to the implementation of the PMTPT and research priorities (created using BioRender.com). PMTPT = programmatic management of TPT; TPT = TB preventive therapy.

vaccination coverage (especially if given after infancy), the two tests perform equally well for prediction of future disease.^{5,14} Reduced access to both tests delays the roll-out of PMTPT, particularly in household contacts aged ≥ 5 years, where testing for TBI is desirable to maximise benefit over risk. The availability of many products and formulations fragment the market and affect supply channels and costs. At the meeting, a Global Drug Facility representative explained that the consolidation of standards or recommendations for preferred formulations and tools would facilitate competition, lower prices and optimise access to high-quality products.

Research gaps

Improved procurement and life cycle management of new and old tools, and financial support for procurement and technical assistance will expedite the introduction of new products. The goal would be to simplify the set of elements that are needed to deliver TPT under field conditions, such as screening tests, diagnostics, data collection systems (especially for household contact investigations) and medicines (including consolidation of regimens and formulations for TPT).

Financing

Barriers

The ongoing shortfall of funds for PMTPT is anticipated to persist in the coming years in middle- and high-burden countries. This need was noted at the expert meeting, prior to the onset of the COVID-19 pandemic in March 2020. The global pandemic of COVID-19 has resulted in major reallocation of budgets, equipment and staff from TB frontline work to pandemic mitigation, exacerbating the problem of limited funding for TPT (see section below on “Reflections after the meeting”). The financing landscape for TPT is gradually shifting from donor-funded to government-funded. Going forward, TB prevention should continue to be financed through domestic resource mobilisation, and increasingly as part of reforms for universal health coverage or innovative schemes for market shaping and social impact bonds. In countries adopting universal health-care systems, there is an opportunity to expand TPT provision through these new systems by allowing diagnosis and treatment by providers who are not part of TB programmes. This would be feasible only if TPT is very safe and easy to complete, and if the diagnosis of TBI (including the exclusion of TB disease) is simplified.

Research gaps

Data on PMTPT financing and coverage under national health services or health insurance schemes are needed. A priority for research is the development and testing of incentivised models of TPT delivery in

different countries and the identification of effective models of care provision and payment.

The perspective of persons infected with M. tuberculosis

Barriers

The voices of the persons infected with *M. tuberculosis* has not been systematically integrated into research. Information is lacking on how people perceive risk, how they understand a diagnosis of TBI and how much value they place on preventing TB disease.

Research gaps

Qualitative research such as focus group discussions and in-depth interviews with key informants is needed to understand acceptability of testing, use of different algorithms of varying complexity for investigation, and the trade-offs of convenience, opportunity cost, duration and safety of preventive treatment. It is also important to understand perspectives of patients in different settings and from different target populations regarding these issues.

Barriers and research priorities related to the cascade of care

Step 1: Identification and linkage to care

Barriers

From an operational perspective, the initial step of identifying people who would benefit from TPT is an important barrier. Evidence on finding target populations and linking them to care is contradictory: in some studies, home visits were essential in identifying and linking persons to care,^{15,16} but other studies reported that home visits had little impact, as the greater number of persons identified did not result in greater numbers successfully taking treatment.¹⁷

Research gaps

Epidemiological research should concentrate on refining estimates of risk to identify persons and groups at highest risk of progression to active TB disease. Modelling studies and qualitative research could be used to increase understanding of the impact of different strategies for linkage to care in different contexts.^{18,19} More information on research priorities is provided in Table 2.

Step 2: Testing for TB infection

Barriers

There is a worldwide shortage of quality-assured PPD reagents for TSTs for TBI and very few countries have a local manufacturer of PPD. Only a limited number of middle- and high-burden countries currently use IGRAs due to the high cost of the test, and the need for associated systems for sample transportation, equipped laboratories and skilled human resources in these laboratories. The major limitation of current

Table 2 Research gaps organised by steps in the PMTPT cascade of care

Cascade step	Research gaps
Step 1: Identification and linkage to care	<ul style="list-style-type: none"> • Best approaches for linkage to care – examining HIV services, child care services and family health or primary care services • Characterise the impact of different strategies in different contexts (modeling studies) • Identify acceptability and feasibility of different treatments and models of care (qualitative research)
Step 2: Initial evaluation (testing for TB infection)	<ul style="list-style-type: none"> • Re-evaluation of cost, feasibility, yield and cost-effectiveness of testing for TB infection among household contacts aged ≥ 5 years • Assessment of the benefit of tests for TB infection in PLHIV on ART and/or in settings with lower rates of TB incidence and transmission defined as those with a TB notification rate of < 100 TB cases (all forms) per 100,000 population and year • Evaluation of more specific TB skin tests and point-of-care IGRA tests when they become available (sensitivity, specificity, predictive ability, and operational cost and feasibility in primary care settings) • Longer term: deeper understanding of mechanisms of latency to identify biomarkers of progression
Step 3: Medical evaluation to exclude TB disease and recommend TPT	<ul style="list-style-type: none"> • Evaluation of software for the computer-aided detection of TB on digital CXR, especially in specific risk groups (i.e., children, PLHIV) • Cost-effectiveness and feasibility of expanding digital CXR in primary care settings in high and intermediate incidence countries • Cost-effectiveness of expanded CXR access, and evaluation of payment for CXR through general health services • Longer term: development and assessment of alternative methods to exclude TB disease
Step 4: TPT	<ul style="list-style-type: none"> • Evaluation of regimens of 1–2 months' duration for efficacy, safety, tolerability and acceptability • Patient and provider attitudes to TPT and ways to overcome barriers to acceptance of treatment • How to accurately monitor and track adverse events related all TPT regimens in programmatic settings • Evaluation of safety of all TPT regimens in pregnant and breastfeeding women • Longer term: shorter regimens and/or long acting single-dose regimens (for example 'depot' injections of a long-acting agent)

PMTPT = programmatic management of TPT; PLHIV = people living with HIV; ART = antiretroviral therapy; IGRA = interferon-gamma release assay; CXR = chest X-ray; TPT = TB preventive therapy.

tests for TBI is their poor predictive value for future TB disease; the resultant need to treat large numbers of persons to prevent relatively few cases of TB critically impacts the cost-effectiveness profile of the entire cascade, as well as individual risk-benefit considerations. New TSTs and IGRAs are expected to come on the market soon.^{20,21}

Research gaps

Market shaping research is essential to improve availability of tests, including demand creation. In the short term, research should focus on re-evaluating testing for TBI using currently available tests in at-risk populations. Studies that can quantify the balance of benefit to harms of giving TPT with and without testing for TBI in contacts aged ≥ 5 years would be helpful to inform local policies. The development and evaluation of biomarkers for disease progression is a high priority, as is implementation research to identify the most efficient pathways for use of the new diagnostic tests for TBI. More information on research priorities is provided in Table 2.

Step 3: Medical evaluation to exclude TB disease and recommend TPT

Barriers

The optimal approach to exclude TB disease prior to initiating TPT remains a challenge in most high and

intermediate incidence countries. Many TB programmes rely on symptom screening; however, this has adequate sensitivity only in people living with HIV infection who are not receiving antiretroviral therapy (ART), but has unacceptably low sensitivity in all other groups. Any abnormality on chest X-ray (CXR) has a 94% sensitivity, making it a useful tool for the exclusion of TB disease in asymptomatic candidates for TPT.²² Among the barriers to broader use of CXR are a shortage of trained technicians to perform the X-ray and qualified personnel to interpret them. The high cost for equipment and materials result in high costs per test, which are usually paid by the patient, constituting a major barrier. Digital radiography has lower operating costs, no film processing and decreased radiation, and can be interpreted remotely by experts, but has high initial capital costs. Use of computer-aided detection (CAD) for pulmonary TB screening could replace human readers, and there are several commercially available CAD software programmes for this. However, to date these are costly, due to high licensing and per-use fees. Moreover, more evidence is required regarding which algorithms to use, whether to use machine learning or deep learning and how to optimise the use of human interpretation to improve specificity.²³

Table 3 Research gaps for high-risk populations

Population	Research gaps
PLHIV	<ul style="list-style-type: none"> • Re-evaluation of the benefits and risks of TPT with or without testing for TB infection in PLHIV of different ages and in diverse epidemiological settings • Pharmacokinetic studies of new TPT regimens • Further evaluation of safety and drug-drug interactions in those on ART • Further evaluation of safety in pregnant women with HIV • Assess whether repeated courses of short course regimens are needed in settings with high TB transmission, and if so, how frequently
Household contacts aged ≥ 5 years	<ul style="list-style-type: none"> • Understanding the advantages and disadvantages, from individual and public health perspectives, of testing for TB infection using current or new tools • Understanding the epidemiological impact of treating household contacts of varying age ranges • Evaluating the public health benefits in terms of active case-finding • Evaluate models for access to care, linkage to care and models of care for community delivery of TPT • Development and assessment of more efficient and effective diagnostic algorithms to rule out TB disease • Research to find ways to enhance acceptance • Research to assess if other close contacts (e.g., workplace or neighbourhood) should also be considered for TPT
Household contacts under 5 years	<ul style="list-style-type: none"> • Access to care, particularly overcoming barriers such as stigma and beliefs of parents • Best methods to rule out TB disease • Child-friendly formulations for TPT, particularly HP combinations • Safety and tolerability of the currently available shorter HP regimens • Drug-drug interactions between shorter regimens and paediatric ART or malaria medications
Other people at risk	<ul style="list-style-type: none"> • Evidence on the likelihood of progression from infection to TB disease in people with the following risk factors: diabetes, harmful use of alcohol, tobacco smoking, underweight, silica exposure, on steroid treatment, rheumatological disease and cancer • Studies of efficacy and adverse events of shorter, better-tolerated treatment regimens in certain risk groups (e.g., people who use drugs, people who engage in harmful use of alcohol and older persons) • Service delivery models to improve management, including the provision of additional interventions to smokers, harm reduction services for people who use drugs or who engage in the harmful use of alcohol and those in prison

PMPT = programmatic management of TPT; PLHIV = people living with HIV; ART = antiretroviral therapy; HP = isoniazid + rifampin; TPT = TB preventive therapy.

models of care for community delivery of TPT, including digital adherence technologies. The evaluation of alternative mechanisms for linkage to care, such as involving primary care providers or community health workers is also a research need for this high-risk population. An important challenge is acceptance and safety of TPT, particularly among adult contacts. Finally, research is needed to assess if other close contacts (e.g., workplace or social) should also be considered for TPT, as is done in some low-prevalence countries, particularly if active case-finding is done among these populations.

Household contacts aged <5 years

Generally, the research priorities for household contacts under 5 years, are the same as those identified for household contacts aged ≥ 5 years, with a few additional areas. These include access to care, particularly overcoming stigma and beliefs of parents who may be hesitant to initiate their children on TPT, and the best methods to rule out TB disease in view of the well-known difficulties of CXR interpretation in young children. Priority should also be given to the currently available shorter HP (isoniazid + rifampin) regimens, including the development of child-friendly formulations, safety and tolerability, and potential drug-drug interactions between these regimens and paediatric ART or malaria medications.

Other people at risk

The WHO does not currently recommend systematic testing for TBI and TPT for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people, as there is a paucity of data from clinical trials on the benefits and harms of TPT. Evidence on the likelihood of progression from infection to TB disease is needed for these populations, as well as those exposed to silica, those on steroid treatment, those with rheumatological disease or cancer and indigenous populations. In addition, studies of efficacy and adverse events of shorter, better-tolerated treatment regimens are needed for certain risk groups (e.g., people who use drugs, people who engage in harmful use of alcohol and older persons). Finally, research should evaluate service delivery models to improve the management of TPT, including the provision of additional interventions to smokers, harm reduction services for people who use drugs or who engage in the harmful use of alcohol and those who are incarcerated (Table 3).

REFLECTIONS AFTER THE MEETING

In March 2020, the world changed with the spread of SARS CoV-2 and the declaration by the WHO of a global health emergency. As COVID-19 spread,

health infrastructure and resources have been reattributed, leaving already underfunded TB programmes vulnerable.^{27–29} The impact on individuals with TB and available services has been immediate, as TB notifications fell by 88% in the Global Fund-implementing countries, and the number of individuals initiating TB treatment were substantially reduced.³⁰ The longer-term epidemiological impact on TB is not yet clear; however, preliminary modelling studies suggest an anticipated 6.3 million added cases and 1.4 million additional deaths between 2020 and 2025.³¹ In September 2020, the UN Secretary General's report of progress toward meeting the 2018 UNHLM targets³² made two recommendations for TB prevention: 1) dramatically scale up provision of TPT, and 2) ensure that TB prevention and care are safeguarded in the context of COVID-19 and other emerging threats.

CONCLUSIONS

TPT is an essential intervention towards achieving the goals of the End TB Strategy. Given the absence of a scalable, effective vaccine, it is of paramount importance in the short and medium term. Conceptualisation of the cascade of care for TB prevention provides a framework to systematically analyse the barriers and enablers of the approach. Since 2018, pivotal achievements include the development and assessment of shorter and safer treatment regimens, and the adoption of a full package of TB care and prevention interventions for PLHIV. Guidelines for the roll out of TB prevention activities have been developed by the WHO.

In order to reach the End TB goals, research to support scale up of PMTPT must be strengthened, with priority given to several areas identified in this meeting. Strengthened biomedical research is needed to develop better diagnostics and treatment regimens, research into models of service delivery, particularly for adult contacts, is critical to expand TPT, and strengthened behavioural science is needed to understand attitudes and beliefs of persons who could benefit from TPT. Stimulating and investing in research will be pivotal to support PMTPT scale-up to reach the UNHLM targets.

Although COVID-19 has ravaged health systems across the world, it has also presented several opportunities for TB programmes. Advances in digital technologies may be leveraged by TB programmes to support TPT. There may be greater opportunities for systematic screening for TB and TBI of individuals presenting with symptoms suggestive of COVID. Looking for these and other synergies may be helpful to rebuild programmes that have been derailed by the COVID pandemic. A major effort to redirect human and financial resources back into TB

programmes is needed to ensure that PMTPT can achieve the UNHLM targets.

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R É S U M É

CONTEXTE : En 2018, les états membres de l'OMS se sont engagés à fournir un traitement préventif antituberculeux (TPT) à au moins 30 millions de personnes d'ici 2022. Cependant, seuls 6,3 millions de personnes avaient été mises sous TPT à la fin de l'année 2019. Le manque considérable de connaissances et les besoins importants en recherche en matière de diagnostic, de traitement et de prise en charge programmatique du TPT (PMTPT) doivent être comblés sans attendre.

MÉTHODES : En septembre 2019, un groupe de parties prenantes engagées dans la PMTPT dans les pays à forte incidence de TB s'est réuni pour formuler un plan d'action afin de soutenir l'expansion mondiale de la PMTPT.

RÉSULTATS : Des obstacles au niveau des systèmes de santé, ainsi que des priorités de recherche afin de

surmonter ces obstacles, ont été identifiés à chaque étape de la cascade de la PMTPT. Le besoin de données relatives au financement du TPT, les lacunes et la couverture des soins par les régimes d'assurance maladie nationaux, ainsi que les besoins en modélisations mathématiques et coût-efficacité de l'impact du TPT sur l'incidence et la mortalité de la TB ont été mis en évidence. Des besoins particuliers en matière de recherche ont été identifiés pour les groupes de population à haut risque tels que les contacts domestiques de tout âge et les personnes vivant avec le VIH, ainsi que pour d'autres personnes à risque.

CONCLUSIONS : La réunion a permis de faciliter la prise de décisions relative à un ensemble d'actions nécessaires afin de garantir l'expansion de la PMTPT dans le but d'atteindre les objectifs de la Stratégie de l'OMS pour mettre fin à la TB.
