World Health Organization
REGIONAL OFFICE FOR South-East Asia

TO END TB, PREVENT TB

PROGRAMMATIC MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

SOUTH-EAST ASIA REGIONAL ACTION PLAN

World Health Organization

REGIONAL OFFICE FOR South-East Asia

PROGRAMMATIC MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

SOUTH-EAST ASIA REGIONAL ACTION PLAN

South-East Asia Regional Action Plan on Programmatic Management of Latent Tuberculosis Infection

ISBN: 978-92-9022-721-2

Suggested citation. South-East Asia Regional Action Plan on Programmatic Management of Latent Tuberculosis Infection. New Delhi: World Health Organization, Regional Office for South-East Asia; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

CONTENTS

BOXES

DIAGRAMS

GRAPHS

TABLES

ABBREVIATIONS

3HP	once a week treatment with isoniazid and rifapentine for 3 months
3HR	isoniazid and rifampicin daily for 3 months
6H	isoniazid daily monotherapy for 6 months
9H	isoniazid daily monotherapy for 9 months
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ATT	anti-TB treatment
CBO	community-based organization
CHW	community health worker
CSR	corporate social responsibility
CSO	civil society organization
CXR	chest radiography
DALY	disability-adjusted life year
DOT	directly observed therapy
DR-TB	drug-resistant TB
FDC	fixed dose combination
HCP	isoniazid, co-trimoxazole and pyridoxine
HIV	human immunodeficiency virus
HP	isoniazid and rifapentine
HR	isoniazid and rifampicin
ICT	integrated counselling and testing
IDU	injecting drug user
IGRA	interferon gamma-release assay

INH	isoniazid
IPT	isoniazid preventive treatment
KAP	knowledge attitude practice
LTBI	latent TB infection
MDR-TB	multidrug-resistant TB
MO	medical officer
MoH	Ministry of Health
Mtb	*Mycobacterium tuberculosis*
NTP	national TB control programme
OST	opioid substitution therapy
PITC	provider-initiated testing and counselling
PLHIV	people living with HIV
PWID	people who inject drugs
QALY	quality-assured life year
QFT-GIT	quantiFERON®-TB gold in-tube test
Rif	rifampicin
RMNCAH	reproductive, maternal, newborn, child and adolescent health
RPT	rifapentine
SAT	self-administered therapy
SEA Region	South-East Asia Region
T-Spot	T-SPOT®.TB test
TB	tuberculosis
TNF	tumour necrosis factor
TPT	TB preventive treatment
TST	tuberculin skin test
UNHLM TB	United Nations High-Level Meeting on TB
UN	United Nations
VCTC	voluntary counselling and testing centres
WHO	World Health Organization

KEY DEFINITIONS

The following definitions apply to the terms used in this document; they may have different meanings in other contexts.

Adolescent	A person 10–19 years of age
Adult	A person older than 19 years of age unless national law defines a person as being an adult at an earlier age
Bacteriologically confirmed TB	TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert MTB/RIF
Child	A person under 10 years of age
Contact	Any person who was exposed to a patient with TB (it has further subclasses of household contacts as mentioned below)
Contact investigation	A systematic process for identifying previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal includes testing for latent TB infection (LTBI) to identify candidates for preventive treatment. Contact investigation consists of identification, prioritization and clinical evaluation
High TB-incidence country	A country with a WHO-estimated TB incidence rate of ≥100/100 000 population
Household contact	A person who shared the same enclosed living space as the index patient for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment

Index case (index patient) with TB	The initially identified case of new or recurrent TB in a person of any age, in a specific household or other comparable setting in which others may have been exposed. An index case is the patient on whom a contact investigation is centred, but who is not necessarily the source case
Infant	A child under 1 year of age
Latent tuberculosis infection	A state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no clinical manifestations of active TB. There is no gold standard test for direct identification of M. tuberculosis infection in humans. The majority of infected people have no signs or symptoms of TB but are at risk for developing active TB disease
Low TB-incidence country	A country with a WHO-estimated TB incidence rate of <100/100 000 population
Preventive treatment	Treatment offered to individuals who are infected with TB bacillus and considered to be at risk for TB disease, in order to reduce that risk. Also referred to as LTBI treatment or preventive therapy
Tuberculosis	The disease state due to *M. tuberculosis.* In this document, it is commonly referred to as "active" TB or TB "disease" to distinguish it from LTBI

FOREWORD

The theme of World TB Day of 2019 – "It's time" – highlighted an important point: that the drive to End TB has reached a critical phase, globally and in the South-East Asia Region that bears a disproportionate burden of the disease.

The political commitment to End TB across the Region is at its peak. In March 2017, Member States issued a Call for Action, underscoring the political, technical and strategic interventions needed to end the disease, and matching this, WHO Regional Office for South-East Asia made "accelerating efforts to End TB by 2030" as its Regional Flagship Priority. In March 2018, at the WHO-supported Delhi End TB Summit, Member States unanimously adopted a Statement of Action pledging to intensify efforts towards ending TB by or before 2030.

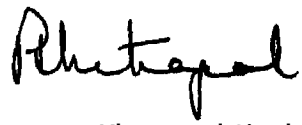
Importantly, Member States reaffirmed their commitment during the UN General Assembly's High-Level Meeting on ending TB by adopting key targets related to diagnosis, treatment and prevention along with commensurate resource mobilization in October 2018.

Global- and regional-level scientific evidences clearly indicate that the required rate of decline in TB incidence can be achieved only if the treatment of active TB disease is combined with the treatment of TB infection (preventive treatment). Preventive treatment is not only a standard of care, but a cost-effective intervention that will also reduce TB-related mortality and avert disability-adjusted life years (DALYs), thus contributing to socioeconomic development.

The South-East Asia Region has the highest burden of TB infection with an estimated 587 million people infected with *Mycobacterium tuberculosis* with a potential to get active TB disease in their lifetime, which is especially higher in the first two years of acquiring the infection. Comorbid conditions existing in the Region such as malnutrition, HIV, diabetes, interstitial lung diseases, problem alcohol use and smoking contribute to increase the risk of conversion to active TB disease.

To equip the Member States in the fight against tuberculosis, WHO Regional Office for South-East Asia has developed this Regional Action Plan for the Programmatic Management of Latent TB Infection (LTBI) in consultation with stakeholders, civil society and community partners, and technical experts – in line with WHO's updated and consolidated LTBI treatment guidelines of 2018. This Action Plan aims to assist Member States in updating their preventive treatment policies and prepare the health and community systems adequately to reach out to the "at-risk" people who need preventive treatment most, such as children under-5 with a patient with TB in the family, people living with HIV, other close contacts of patients with TB and risk groups, such as prisoners contextualized to local epidemiology.

I hope that all Member States will gear up their systems for a rapid scale up of TB preventive treatment services to further consolidate our efforts and actions to end TB in the Region.



Dr Poonam Khetrapal Singh
Regional Director
WHO South-East Asia Region

EXECUTIVE SUMMARY

Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB. Although individuals with LTBI do not have active TB disease, they may develop the disease in future, making the person ill and putting them at risk of passing the infection to other people. The WHO End TB Strategy requires diagnosis and treatment of LTBI at a wider scale along with concerted efforts of management of all forms of active TB diseases to accelerate the decline in TB incidence. Such a combined package of curative and preventive treatment of TB is cost-effective in decreasing the rate of TB incidence, disability-adjusted life years (DALYs) averted and lives saved. The targets committed to by Member States as part of the Political Declaration at the United Nations High-Level Meeting (UNHLM) on TB (September 2018) include treating 40 million patients with TB and 30 million people with LTBI by 2022. World Health Organization (WHO) updated the guidelines for programmatic management of LTBI in 2018 to assist Member States in strengthening their capacities and systems to tackle LTBI with shorter and safer treatment regimens. Member States in the South-East Asia (SEA) Region have also made commitments to mobilize additional resources to enhance TB preventive treatment (TPT) in their respective countries.

The SEA Region bears more than 40% of the global burden of incident TB cases including almost 35% of the LTBI burden of the world. This is starkly disproportionate to only about 26% of the global population that lives in the Region. The current response to the TB situation in the SEA Region needs to be accelerated urgently if significant progress is to be made towards achieving the targets of the End TB Strategy.

Accelerating efforts to End TB by 2030 is a Regional Flagship Priority. To make a real dent in the TB epidemic, preventive treatment must become a key priority, in addition to accelerating TB case-finding and treatment. To align with the

global commitments made at the UNHLM on TB in September 2018 by Member States, the Region needs to reach and treat at least 10.5 million people with LTBI by 2022. This will require urgent and rapid scaling up of access to TB preventive treatment (TPT).

The WHO Regional Office for South-East Asia, in consultation with Member States, technical partners, community representatives and individual experts, has prepared this document for the scale up of programmatic management of LTBI. It aims to support the Member States in developing clear policies and targets, while helping to address operational modalities.

It is conservatively estimated that there are 15 million people in the SEA Region who are eligible for TPT as per the WHO 2018 guidelines for programmatic management of LTBI. These people are likely to have been recently infected (within past few months) and have the highest probability of going on to develop active TB disease. Treating this pool of people living with recently acquired TB infection will help to reduce the incidence of TB by an additional 12-15% per year, or about 270 000 fewer TB cases each year over and above what can be achieved by improving diagnosis and treatment of active TB. If the coverage of this intervention is rapidly scaled up within the next 3 years, it will prevent more than 1 356 569 new TB cases in the Region and avert more than 2.3 million DALYs by 2025. With an anticipated massive cost reduction of new and safer drugs, preventive treatment will become highly cost-effective, with less than US$ 400 per DALY averted on average across the Region, and these costs are expected to get lower as the programmatic management of LBTI scales up.

BACKGROUND

WHAT IS LATENT TB INFECTION (LTBI)?

Infection with *Mycobacterium tuberculosis* (*Mtb*) is the precursor to tuberculosis (TB) disease, which is responsible for 1.5 million deaths each year – more than any other infectious disease. Once infected, the individual is at highest risk for developing TB disease within the first two years but can remain at risk for their lifetime. In 2014, the global burden of latent TB infection (LTBI) was 23%, amounting to approximately 1.7 billion people *(1)*.

As the global community gears up to meet the ambitious targets for reduction (90% reduction in TB incidence by 2035) and even elimination of TB (less than 1 incident case per 1 000 000 population per year) by 2050 in some countries, our ability to address the LTBI reservoir will be critical in our effort to succeed in the absence of vaccines and other preventive interventions that can be scaled up in the short term.

LTBI is a "state of persistent immune response to stimulation by *Mtb* antigens with no clinical manifestation of active TB" (Box 1).

Box 1

Persons with latent TB infection (LTBI)

- Have in his/her body TB bacteria which are alive but not causing disease.
- Do not feel unwell and do not have symptoms.
- Usually have a positive skin test or blood test result indicating TB infection but may have a normal chest X-ray and a negative sputum test and negative Xpert MTB/RIF® test.
- Without treatment, 5–10% of infected persons will develop TB disease at some time in their lives. About half of those people who develop TB will do so within the first two years of infection.
- For persons whose immune systems are weak, especially those with HIV infection, malnutrition, on anti-cancer therapy, or on dialysis, the risk of developing active TB disease is considerably higher than that for persons with normal immune systems.
- Risk of progression to active TB in people living with HIV (PLHIV), and household contacts of infective patients with TB can be reduced by providing them with TB preventive treatment (TPT).

LTBI DRIVES THE TB EPIDEMIC

The progression from LTBI to active TB disease among the 1.7 billion population infected with TB *(1)* continues to add to the existing number of TB patients every year. Several scientific studies suggest that a major driving force behind both occurrence and recurrence of TB may be reactivation of LTBI. A systematic review of 11 studies of South-East Asia revealed that 24.4% to 69.2% of children under 15 years of age who were exposed to TB in their households were infected with TB and 3.3% to 5.5% had developed active TB *(2)*. A hospital-based

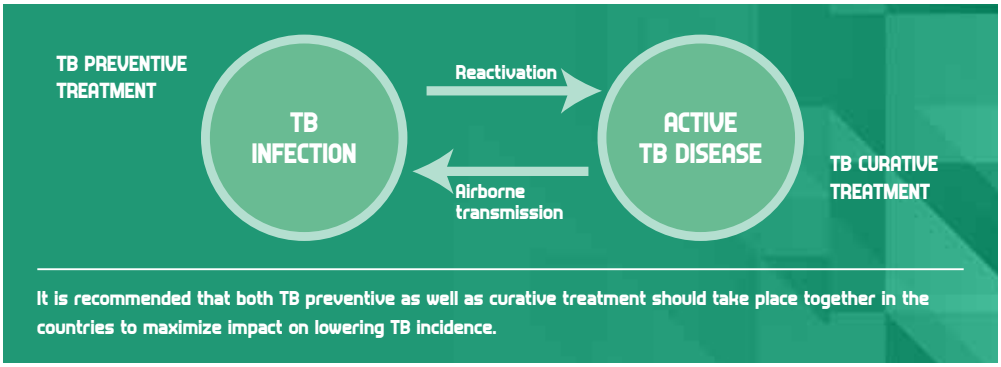
A major driving force behind both occurrence and recurrence of TB may be reactivation of LTBI.

study in a major chest hospital of China showed that 64% of recurrent TB cases were due to reactivation of latent infection *(3)*. A similar study in Spain showed that only 50% of the recurrent cases were due to reinfection whereas the remaining were due to reactivation *(4)*. The host factors increase an individual's risk of progression to active pulmonary disease after LTBI. Host-related determinants of risk for disease include HIV infection, diabetes, smoking, excess alcohol use and malnutrition.

RATIONALE OF TB PREVENTIVE TREATMENT (TPT)

The benefit of preventing individuals from progressing to active TB, especially those at high risk of reactivation, is widely accepted today. Well-designed clinical trials have validated several regimens as effective and safe ways to prevent progression to TB disease. In low-incidence settings, management of latent infection can contribute to elimination of the disease. A review of treatment regimens found that the treatment of latent TB can reduce the risk of disease reactivation by 60% to 90% *(5)*. A recent randomized controlled trial in a high TB-burden country showed that the benefits of preventive treatment in people living with HIV (PLHIV) can last for more than 5 years *(6)*. TB preventive treatment (TPT) provides not only individual protection against active TB disease but also regular treatment to the at-risk people. These include essentially the household contacts and PLHIV – which will help in reducing the burden of TB infection in the community, especially in high TB-incidence settings; subsequently lowering the progression of active TB and in turn the new and relapse TB cases (Diagram 1).

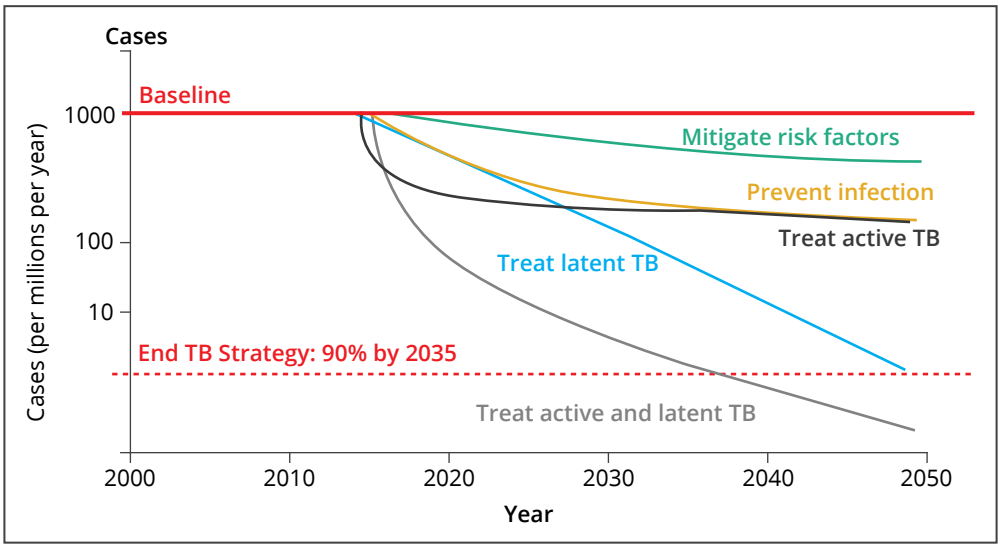
Diagram 1. The vicious cycle of TB infection and active TB disease



Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy (6). WHO has published updated and consolidated guidelines for programmatic management of LTBI in 2018, which offer recommendations for preventive treatment, including with newer drugs that need shorter treatment durations, are well tolerated and thus have better efficacy due to improved adherence. The End TB targets, as committed to by Member States, cannot be achieved without addressing LTBI at scale. However, prevention has received little priority due to multiple supply- and demand-side barriers.

Member States are committed to the WHO End TB Strategy, of which prevention of active TB disease by treatment of LTBI is a critical component.

Graph 1. LTBI management contributes to the targets of the End TB Strategy[i]



Source: Dye et al. *(7)*

Dye et al. *(7)* conclude that eliminating TB requires a simultaneous attack on two components of the *Mtb* life-cycle (Graph 1):

- cutting transmission by treating active cases
- neutralizing the reservoir of latent infection, by preventing activation in high-risk groups.

This study presumes mass preventive treatment based on a biological marker of progression, a tool that is not yet available. However, this provides an indirect evidence that preventive treatment should be offered to at least high-risk groups using the current tools to reap the benefits of available treatments.

To summarize, the targets of ending TB can be achieved only by combining the effective treatment of active TB, which involves early case detection, with high cure rates to interrupt transmission, along with methods to prevent new infections and to neutralize existing latent infections using preventive treatment.

i The baseline represents all TB cases while the other lines represent impact of intervention/s. Maximum decline is observed by a combination of treating active TB and latent TB i.e. both interventions together.

TPT AS PART OF THE PACKAGE OF TB SERVICES

TPT is not a stand-alone activity; rather it should be implemented within the overall package of services of the national TB control programme (NTP) and using the resources within the health system. This is the only realistic, feasible and cost-effective option to scale up TPT.

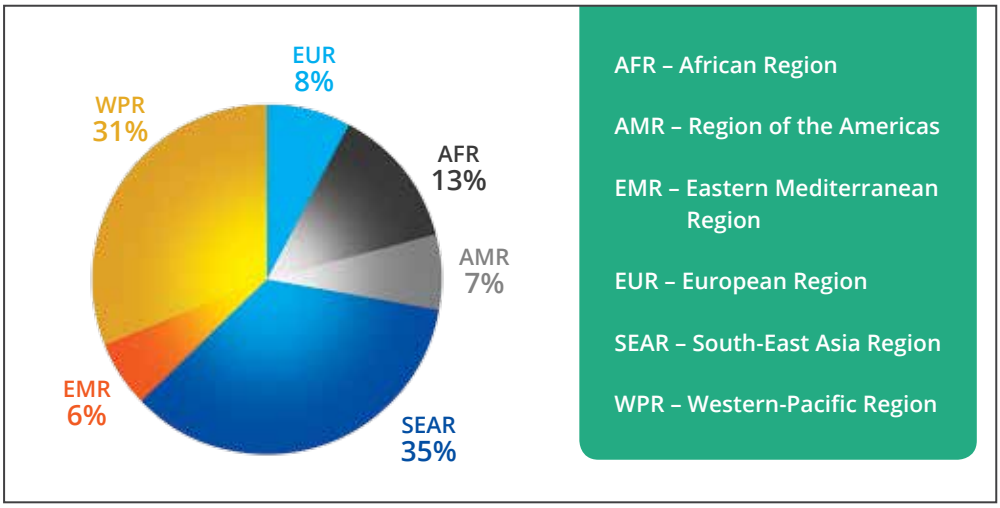
A recently notified TB patient and his/her household contacts including children should be regarded as one whole unit of beneficiaries of NTP services where those with active disease should be initiated on anti-TB treatment (ATT) and the rest commenced on TPT. The monitoring of treatment adherence can be done together for all of them in the unit by using the same resources to ensure successful completion of ATT by the patient/s with TB and TPT by the healthy, yet infected contacts. On similar lines, PLHIV must have access to TPT services as part of their continuum of care at the ART (antiretroviral treatment) centres, counselling centres and existing community-based HIV projects.

Demand generation and advocacy for TPT can be integrated with the overall community engagement strategies of NTP with active involvement of the affected community members and partners of civil society organizations (CSOs).

CURRENT SITUATION, RESPONSE AND CHALLENGES OF LTBI IN THE SEA REGION

Around 587 million out of the total estimated 1.7 billion people infected with TB globally live in the SEA Region (Graph 2). The SEA Region bears 35% *(1)* of the total global burden of LTBI. About 43.3 million out of 587 million people living with LTBI in the SEA Region are children under 15 years of age (7%) *(1)*. The detailed estimation of population eligible for TPT in the SEA Region is explained in section 3.2.1.

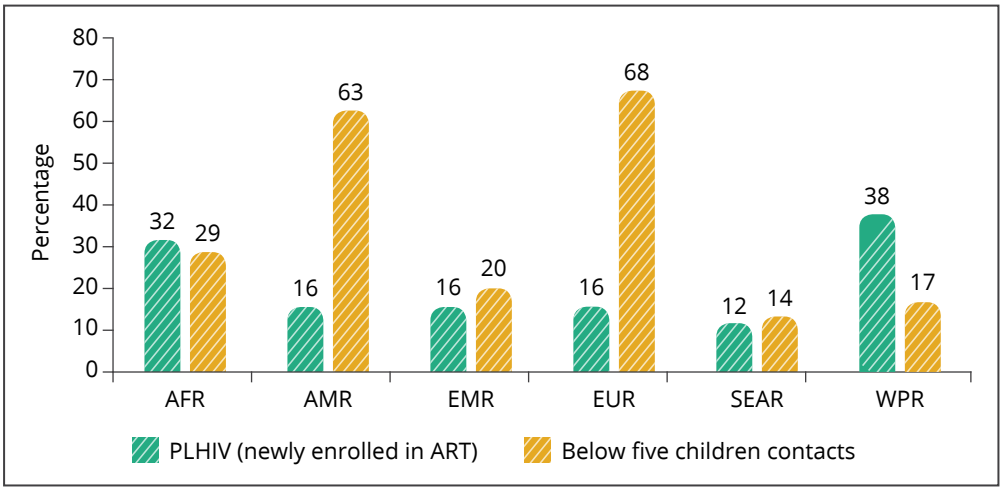
Graph 2. Estimated proportion of people infected with TB, by Region



Source: Global TB Report 2018

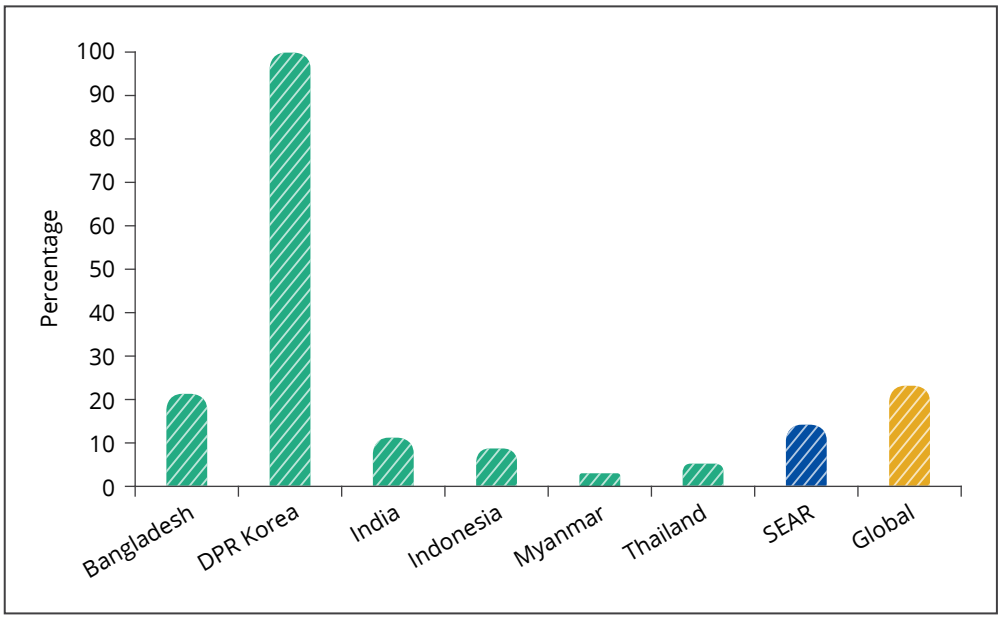
Coverage of TPT: The countries of the SEA Region presently report the TPT coverage of two key target groups, namely, a proportion of PLHIV who are newly enrolled for ART and a proportion of children under 5 years who are household contacts. The TPT coverage among both the groups remains substantially low. Only 12% of the PLHIV who are newly enrolled in care and 14% of children (under 5 years) who are household contacts of bacteriologically confirmed TB cases were put on TPT in 2017 in the SEA Region (Graphs 3 and 4).

Graph 3. Regional TPT coverage



Source: Global TB Report 2018

Graph 4. Country-wise TPT coverage of children under 5 years in high-burden countries



Source: Global TB Report 2018

The Region has faced challenges to expansion of TPT services. However, with recent improvements in drug regimens and a more nuanced understanding of the importance of prevention, new opportunities have presented themselves. Some of these are discussed in Box 2.

The SEA Region has faced challenges in expansion of TPT services. In 2017 only 12% of the PLHIV who are newly enrolled in care and 14% of children under 5 years who are household contacts were put on TPT.

Box 2

Challenges and opportunities to scale up TPT in the SEA Region

Policy level

- The existing policies on the coverage of risk groups for TB preventive treatment (TPT) are already partially aligned with the latest WHO recommendations. With the inclusion of adolescent and adult household contacts of patients with TB, policies of all Member States can become fully aligned with the new WHO guidance.
- All Member States already have access to daily isoniazid (INH) monotherapy for 6 months for TPT and a few also have access to daily 3HR for 3 months. Replacing it with shorter, user-friendly regimens, such as 12 doses of rifapentine and isoniazid (3HP), will make it easier for the health system to administer the regimen and make the treatment more tolerable. There is also the possibility of using a daily HP course for one month. In other words, many safer and shorter options are now available.
- Demand for TPT at the community level needs to be generated by disseminating appropriate knowledge and evidence on the benefits of preventive treatment. Community engagement has been increasing in the Region, and communities can become allies in this endeavour.

Operational level

- Investigation of contacts of index cases for active TB is the backbone of case-finding activities that need to be strengthened in all countries. This also enables reaching out to people at risk for developing the disease, i.e. those with LTBI needing TPT.
- Specifically, for PLHIV, linkages between the HIV and TB programmes for preventive treatment can be strengthened.
- Awareness and knowledge among implementers at the health-care delivery level about the need for preventive treatment need to be

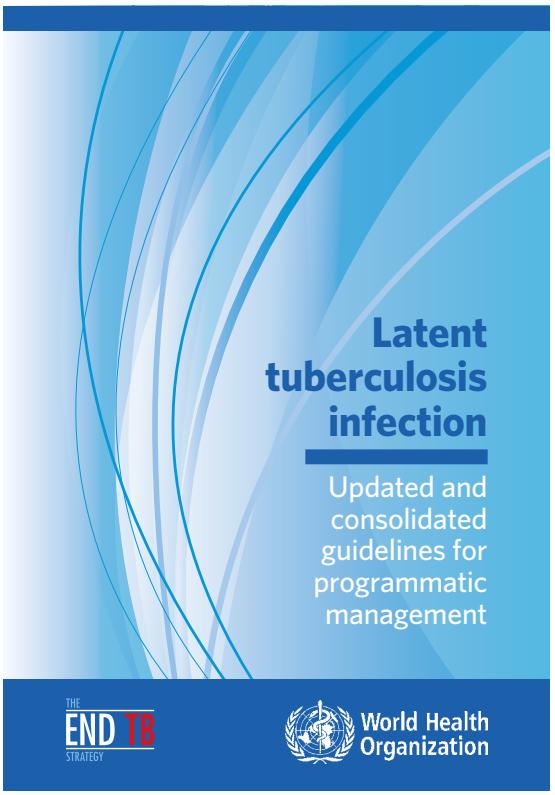
improved, particularly to ensure that various new developments in treatment and diagnostics are widely understood and used. Early detection of TB cases and regular screening of household contacts of index cases of TB opens up opportunities for expanding the TPT services and improving their coverage.

- The non-public health sector and communities offer a big opportunity for the success of preventive treatment programmes through collaborative activities. This includes outreach, counselling, screening and support to those on treatment.

Monitoring

- Member States currently record and report the coverage figure of at-risk populations initiated on preventive treatment. This is segregated into household contacts under 5 years of age and PLHIV, but treatment completion is not recorded or reported. The current recording and reporting formats should be amended to include other risk groups, treatment completion rates and other recommended indicators while taking advantage of electronic recording and reporting systems, with their ever-expanding potential in the Region.

UPDATED AND CONSOLIDATED GUIDELINES FOR THE PROGRAMMATIC MANAGEMENT OF LTBI 2018



ENLISTING THE TARGET GROUPS FOR PREVENTIVE TREATMENT

WHO 2018 updated and consolidated guidelines for programmatic management of LTBI identified the priority groups eligible for TPT (Box 3).

Box 3

Target groups for TPT as identified in WHO LTBI Guidelines 2018

A. People living with HIV (PLHIV)

B. Household contacts of index patients with TB

- Adults, adolescents and children above 5 years
- Children under 5 years

C. HIV-negative adult and child contacts

D. Other HIV-negative at-risk groups

- Patients on anti-TNF (tumour necrosis factor) treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI.
- In countries with a low incidence of TB, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high burden of TB, homeless people and people who use illicit drugs.
- Systematic testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations.

CASCADE OF CARE IN PROGRAMMATIC MANAGEMENT OF LTBI

Box 4 shows the flow of providing TPT and ensuring treatment completion.

Box 4

Cascade of care

1. Identify at-risk people for LTBI testing and treatment (as per Box 3).
2. Evaluate them for active TB and rule out active TB.
3. Test for LTBI (wherever applicable and available).
4. Choose, initiate and continue TPT regimen.
5. Monitor adverse events and treatment adherence.
6. Ensure treatment completion.
7. Record and report – initiation and completion.

RECOMMENDATIONS FOR RULING OUT ACTIVE TB DISEASE

For PLHIV

- Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not have symptoms such as current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status.
- Chest radiography (CXR) may be offered to PLHIV and those on ART, and TPT be given to those with no abnormal radiographic findings.

- Adults and adolescents living with HIV who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases that cause such symptoms. Xpert MTB/RIF should be used as the initial diagnostic test. PLHIV who present any of the four symptoms but in whom active TB is excluded by investigations may be considered for TPT.
- Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a patient of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age.

Role of chest X-ray

- The absence of any symptoms of TB and the absence of abnormal CXR findings may be used to rule out active TB disease among HIV-negative household contacts and other at-risk groups before preventive treatment. It is critical to ensure proper follow up and investigation for TB and other diseases in household contacts with abnormal chest radiographic findings or TB symptoms. Investigations should be done in accordance with national guidelines and evidence-based clinical practice. Contacts in whom active TB is excluded after investigations may be considered for preventive treatment.
- Requirement for CXR should not be a barrier for initiating TPT in PLHIV because of the need for additional resources, in view of the marginal gain in negative predictive value. In general, as combining CXR with screening for symptoms at every visit could represent a considerable burden on the health system as well as on clients, it should be used only to exclude active TB before giving preventive treatment, in accordance with evidence-based clinical practice. The role of CXR in regular TB screening and its optimal frequency is uncertain. Local authorities should define its application and frequency based on their local epidemiology, health infrastructure and availability of resources.

A recent publication based on systematic review and meta-analysis of 24 publications examined the use of symptoms, CXR abnormalities, and combinations of symptoms and CXR in excluding active pulmonary TB before treating for LTBI in high TB burden countries. The analysis concludes that In countries with a high TB burden, the absence of any TB symptom and any

CXR abnormality can be used to exclude active pulmonary TB before initiating treatment for LTBI in household contacts aged ≤5 years, of patients with bacteriologically confirmed pulmonary TB *(8)*.

Adults and adolescents living with HIV who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases that cause such symptoms.

DIAGNOSTIC ALGORITHMS

Diagnostic tests of LTBI – testing criteria as per the WHO guidelines

- Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.[ii] *The availability and affordability of the tests will determine which one will be chosen by clinicians and programme managers. Neither TST nor IGRA can be used to diagnose active TB disease nor for diagnostic workup of adults suspected of having active TB.*
- LTBI testing by TST or IGRA is not an essential requirement for initiating TPT in PLHIV or child household contacts under 5 years.
- In countries with a low incidence of TB, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI.

ii TST and IGRA require a competent immune response to identify people infected with TB and are imperfect tests for measuring progression to active TB disease. The availability issues around TST and high cost and strict laboratory requirements for IGRA can pose operational and logistic challenges.

- Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI.
- In countries with a low incidence of TB, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high burden of TB, homeless people and people who use illicit drugs.
- Systematic testing for LTBI is currently not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in the above recommendations.
- For detailed information on administration of the tests and interpretation of test results, facts sheets of US Centers for Disease Control and Prevention can be consulted (available at https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm)

TREATMENT REGIMENS FOR PREVENTIVE TREATMENT

Guiding principles

These are critical steps to be followed for selecting eligible people for TPT, its monitoring and completion of treatment (Box 5).

Box 5

Guiding principles of TPT

1. TPT to be initiated only after confirmation of absence of active TB by a qualified physician/medical officer of the health system. In some countries, trained health workers exclude TB through symptomatic screening.
2. Close monitoring of adverse events and adherence to treatment.

(Continued)

(Continued)

Box 5

3. Ensure treatment completion.
4. Additional care and attention to PLHIV receiving TPT to select the right treatment regimen and monitor drug interactions with ART if rifampicin/rifapentine is used.
5. Informed consent of the eligible people (parents in case of children) who are selected for TPT and right information on TB, LTBI and their treatment to be given to the families of index patients with TB.

Choice of regimens

Currently recommended treatment regimens for LTBI: TPT research constantly strives for more effective and shorter regimens of treatment with reduced number of doses to ensure better compliance of patients and successful completion of treatment (Box 6).

Box 6

Treatment regimens

1. **3HP** – Once-weekly isoniazid–rifapentine for 12 weeks, total 12 doses for adults, adolescents and children above 2 years who are contacts of bacteriologically confirmed index cases of TB; or **1HP** – a daily dose of HP for one month for adolescents and children above 2 years who are contacts of bacteriologically confirmed index cases of TB; Both these regimen can also be given to PLHIV.
2. **3HR**
   - Daily rifampicin plus isoniazid for 3 months for adult and child contacts – total 90 doses
   - Can also be given to PLHIV who are on rifampicin-friendly ART regimen

(Continued)

Box 6

3. 6H/9H/36H

- Daily INH for 6 months for adult and child contacts and PLHIV – total 180 doses
- Daily INH for 9 months for adult and child contacts and PLHIV – total 270 doses
- Daily INH for 36 months for PLHIV, especially those PLHIV with positive TST – total 1080 doses

4. 3–4R

- Daily rifampicin for 3–4 months for adult and child contacts – 90–120 doses
- This could be an option in low-transmission settings.

All INH-containing regimens provide supplementary vitamin B6 to prevent peripheral neuropathy.

Notes: Treatment of LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, health-care providers may prefer to implement the 6-month regimen rather than the 9-month regimen although 9-month treatment is considered more efficacious. Effort should be made to ensure that patients adhere to LTBI treatment. The 6-month regimen is not recommended for people with HIV/AIDS, children, or people with CXR findings suggestive of previous TB disease *(9)*.

The 3-month regimen of weekly rifapentine plus isoniazid can be administered to patients receiving efavirenz-based ART regimens without dose adjustment, according to a study of pharmacokinetics. Administration of rifapentine with raltegravir was found to be safe and well tolerated. Rifapentine-containing regimens can also be administered with dolutegravir *(10)*.

Recommended dosages of drugs for treatment of LTBI *(11)*

Box 7 gives the dosages of various drugs.

Box 7

Dosages of drugs

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range 7–15 mg)	300 mg
Rifampicin alone, daily for 3–4 months	Adults, 10 mg Children, 15 mg (range 10–20 mg)	600 mg
Isoniazid plus rifampicin, daily for 3–4 months	Isoniazid: adults, 5 mg Children, 10 mg (range 7–15 mg) Rifampicin: Adults, 10 mg Children, 15 mg (range 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Rifapentine plus isoniazid, weekly for 3 months (12 doses)	Individuals aged ≥12 years: isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg >50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

SHORTER REGIMENS FOR TPT

Operational advantages of a shorter regimen

Box 8 enumerates the advantages of using a shorter regimen for TPT.

Box 8

Operational advantages of a shorter regimen

1. Randomized controlled trials have shown that the newest regimen for preventive treatment of 12 weekly doses of directly observed isoniazid and rifapentine (3HP) is as efficacious as that of 9 months of isoniazid, with a greater completion rate (82% vs 69%) *(12)*.
2. Rifapentine-based TPT is safe and well tolerated. Across studies, 3HP appears to pose less risk of hepatotoxicity than IPT *(12)*.
3. It is associated with comparable efficacy and tolerability among children (≥2 years old) *(13)*.
4. It is suitable for patients with HIV who are treated with efavirenz- or raltegravir-based ART *(14)*, including with dolutegravir.
5. Probability of conversion to active TB is lesser in those who received 3HP than those who received INH monotherapy *(15)*.
6. Patients preferred treatment regimens with a shorter length of treatment; a factor that determines patients' acceptance to treatment initiation.[iii]
7. 3HP self-administered treatment (SAT) reduced costs of the health system and increased quality-assured life years (QALYs) compared with serial radiographic surveillance and all other regimens (4R, 3RH, 6H and 9H) except 3HP directly observed therapy (DOT), where self-administration of 3HP is also an appealing option *(16)*.
8. It is cost-saving for extremely high-risk patients and cost-effective for lower-risk patients .

(Continued)

[iii] A discrete choice experimental study showed that participants of the study were consistently in favour of a shorter length of treatment, lower risk of side-effects and higher effectiveness *(14)*.

(Continued)

Box 8

9. 3HP has been shown to reduce costs and has resulted in higher rates of treatment completion than the standard LTBI treatment[iv] *(18)*.
10. In high-burden settings too, 3HP is deemed cost-effective. In the case of a Ugandan HIV clinic, 3HP averted 9 cases of active TB, of 37 that occurred with 9H 1 death (of 466), and 5.8 DALYs over a 20-year time period for every 1000 individuals living with HIV *(19)*.
11. There are regimens, such as 3HR (daily INH and rifampicin for 3 months), which also have high efficacy but much higher number of doses. This regimen is most suitable for child contacts under 2 years where 3HP is generally avoided.

Success stories of shorter regimens

The success story of Bangladesh and Taiwan, especially in rolling out the shorter regimen of TPT such as 3HP, is encouraging (Box 9). Greater number of people were seen to complete the short course treatment by 3HP.

Box 9

Success stories

Bangladesh

The Bangladesh National TB Programme in collaboration with USAID-funded Challenge TB Project undertook a feasibility study for implementation of community-based 3HP preventive treatment among household contacts of 883 patients with drug sensitive TB aged over 2 years, who were enrolled from 12 DOT centres in urban Dhaka. The contacts were screened and evaluated to rule out active TB and initiated on treatment as per a pre-defined algorithm in accordance with WHO recommendations. Incentives to promote

(Continued)

[iv] The Taiwan study reported that the cost–effectiveness ratio with 9H was US$ 15 392/avoided 1 case of TB and US$ 5225/avoided 1 case of TB with 3HP *(16)*.

(Continued)

Box 9

treatment adherence were provided at the time of initiation and on every follow-up visit at month 1, 2, and 3. More than 97% of 1216 contacts initiated on preventive treatment completed the treatment with adverse events being observed in 5% of the study population, mostly being mild. The study concluded that community-based approach of preventive treatment using 3HP is feasible with a potential to scale up at the national level.

Taiwan *(16)*

Completion rate – 3HP vs 9INH; 97.03% vs 87.29%

- Costs of 3HP and 9H US$ 261.24 vs US$ 717.3
- Fewer patients discontinued with 3HP due to adverse events

On the other hand, INH monotherapy was associated with less LTBI treatment completion compared to other regimens due to its longer treatment duration (6 months), 40–50% (20,21).

Box 10

Community-level information guide for shorter regimens

There is a need to raise demand among the community for shorter course regimens such as 3HP for TPT. It is recommended that countries should consider adding 3HP in their treatment regimens of LTBI. This is strategic in the context of the SEA Region because the burden of LTBI is very high and we need to treat a very large number of people in a shorter time where treatment adherence and completion is highly desirable.

LTBI TREATMENT FOR CONTACTS OF PATIENTS WITH MDR-TB

Choosing a treatment option for household contacts of patients with multidrug-resistant TB (MDR-TB) is not simple. Box 11 lists some general guiding principles to treat such contacts for preventing TB infection.

Box 11

Preventive treatment of contacts of patients with MDR-TB

1. Preventive treatment of contacts of patients with MDR-TB should be more individualized than that of other patients, which means their treatment should be based on individual risk assessment. TPT to be given to high-risk contacts such as children, PLHIV or people under immunosuppressive treatment among only household contacts after a careful risk assessment, including intensity of exposure, certainty of the source case, reliable information on the pattern of drug resistance of the index case and potential adverse events.
2. Drugs should be selected according to the drug susceptibility profile of the source case.
3. Confirmation of infection with tests for LTBI is required including the absence of active TB.
4. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.

(Continued)

(Continued)

Box 11

5. Drugs to be used should be preferably fluoroquinolones (e.g. moxifloxacin, levofloxacin) with or without other agents (e.g. ethambutol, ethionamide) provided the index case is not resistant to fluoroquinolones. Fluoroquinolones are contraindicated in small children due to the possibility of retardation of development of cartilage (demonstrated only in animals). Hence risk–benefit analysis needs to be done before administering fluoroquinolones in children.
6. Close monitoring of adverse events and adherence to treatment are essential.
7. Treatment duration is based on clinical judgement – 6/9/12 months.
8. Informed consent of the selected contacts to be obtained.
9. Appropriate health information to be provided to the families of index patients of TB on TB, MDR-TB, LTBI and their treatment.

THE REGIONAL ACTION PLAN

INTRODUCTION TO THE PLAN

The South-East Asia Regional Action Plan for the programmatic management of LTBI has been developed keeping in mind the urgent need to progress towards the End TB goals. Preventive TB treatment will accelerate the decline in incidence, prevent unnecessary suffering and reduce DALYs lost. Treatment for prevention of TB is an element of the standard of care for families and close contacts of patients with TB and PLHIV.

The Regional Action Plan aims to assist Member States and partners (i) to advocate and adopt suitable policies for rolling out TPT services along the lines of WHO guidelines; (ii) to strengthen health system responses to meet the additional operational needs for service delivery and enhance community engagement for demand generation and awareness building for TPT services; (iii) to equip the existing recording and reporting system of the countries with additional data management resources for optimal monitoring and supervision; and (iv) to plan for additional budgetary resources.

The Regional Action Plan is primarily guided by the WHO guidelines for programmatic management of LTBI 2018, and advocates for full coverage as

per these guidelines in 3 years that will help countries not only in achieving the targets committed to in the UNHLM on TB but also exceed them. The Action Plan attempts to arrive at estimates of the eligible TPT groups in alignment with the WHO guidelines for coverage through mathematical modelling. Such country-wise modelling-based estimation of target groups is adjusted with the country's projected trend of TB incidence assuming that TPT will build upon a country's efforts towards strengthening existing services and treat additional patients with TB through intensified case-finding. It is anticipated that activities such as contact investigations and screening of PLHIV will be systematically carried out and active disease ruled out before starting patients on preventive treatment. This should be helpful in developing a realistic coverage and logistic plan to implement TPT across the Region and impact on overall reduction in incidence of TB and mortality and DALYs averted.

The plan estimates year-wise targets for each Member State for different target groups such as household contacts (under-5 children, older children/ adolescents and adults), PLHIV and other at-risk groups as given in the WHO guidelines. The plan envisages that the countries should cover the targets within the proposed time-period, preferably using the new shorter regimen such as 3HP, which has shown higher efficacy, acceptability and completion rate among its users. Member States need to engage with CSOs, affected communities and private health sector for demand generation and promotion of TPT services, especially with the newer regimen such as 3HP, which is emphasized in the plan. Member States are urged to develop an ambitious country-level plan for roll out of TPT with equal commitments from the national governments and donors to reduce the incidence of TB for quicker achievement of End TB targets. The plan also aims to help the countries in strengthening the monitoring system for intensified TPT services.

The Regional Action Plan is primarily guided by the WHO guidelines on LTBI management to support countries not only in achieving the targets committed to in the UNHLM on preventive treatment but also exceed them.

Overall aim of the Regional Action Plan: To support Member States in delivering on the regional and global commitments, and reaching the desired targets of ending TB with expanded coverage of their TB preventive services.

Specific objectives of the Regional Action Plan:

- Establish estimates of targets for TPT in line with the WHO guidelines, and support national policy updates in Member States for programmatic management of LTBI.
- Support operational preparedness for programmatic management of LTBI, including roll-out of the recommended new user-friendly preventive treatment regimen.
- Support country efforts to mobilize the necessary resources for rolling out the Plan.

The Plan assumes that all countries will follow the WHO guidelines for identification of target groups – children, adolescent and adult contacts of patients with TB, PLHIV and those with other immunocompromised conditions that make a person prone to the development of TB disease.

The Plan also assumes that TPT will be fully integrated into the national TB, HIV and maternal and child health (reproductive, maternal, newborn, child and adolescent health [RMNCAH]) programmes while building on the strengths of national programmes to deliver services, and undertake active TB case-finding, specifically investigation of contacts.

TARGETS FOR LTBI COVERAGE AND POTENTIAL ACHIEVEMENTS IN THE REGION

Estimation of eligible population for TPT

As per the WHO 2018 guidelines for programmatic management of LTBI, the eligible population can be estimated using the formulas given in Box 12.

Box 12

Estimation of eligible population for TPT

Total number of household contacts. By definition, this means a person who shares the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment. Therefore, the formula to estimate this population = incidence * proportion of bacteriologically confirmed cases * (average household size – 1). (The number of children is calculated separately, as given below, and later deducted from this number to avoid duplicate counting.) This means that all members living in the same household with the bacteriologically confirmed case could have acquired the infection because of close contact.

Number of eligible children. These are part of the household contacts. Calculations are made separately for this group because of the special focus needed on this group as well as the fact that rifapentine-containing shorter regimens are not currently recommended for children under 2 years of age. Therefore, the formula for calculation would be = incidence * (household size – 1) * proportion of bacteriologically confirmed cases * proportion of children under 5 years.

Out of the above, one third children are assumed to be under 2 years of age.

Number of eligible PLHIV. Although all persons living with HIV are at risk of developing TB and therefore eligible for TPT, it is possible to approach only those enrolled for care under the HIV programme. Moreover, there are no current guidelines for a repeat TPT. Hence, the eligible population is calculated as = new HIV registered for care – those who are already under treatment + new infections – deaths.

Other high-risk groups such as those with silicosis, transplant, those on TNF blockers, and those on dialysis: No specific country-wise data are available. This document assumes that 0.1% of the population

(Continued)

(Continued)

may be at risk for calculations. However, countries may use their own estimates depending on local epidemiology of the disease.

Moreover, in countries with a low incidence of TB, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high burden of TB, homeless people and people who use illicit drugs.

The eligible population for TPT is based on the number of household contacts, eligible children, eligible PLHIV, and high-risk groups such as those with silicosis, transplant, those on TNF blockers, and those on dialysis.

Annexure A gives the country-wise eligible and targeted populations segregated by at-risk groups and treatment regimen as well as scale up options.

Gains from rational investment on TPT: A mathematic model (for details *see* Annexure B) has been developed to predict the prospective gains of rational investment on TPT in the Region, where "what if" scenarios were simulated. The scenarios showed variable anticipated achievements of high coverage of TPT in combination with the accelerated efforts of active TB case detection and treatment in the Region, especially in terms of decline in the incidence of TB, DALYs averted and lives saved (Graph 5). The scenarios are given below.

In Scenario 1, it is proposed to treat a total of 57.5 million out of the total 82.41 million eligible at-risk population for LTBI with full scale up over a three-year period till 2021, which is then maintained till 2025 (Table 1).

In Scenario 2, the treatment target assumes a scale-up period of 5 years that would cover 46 million at-risk people (2019–2023), and maintained till 2025 (Table 2).

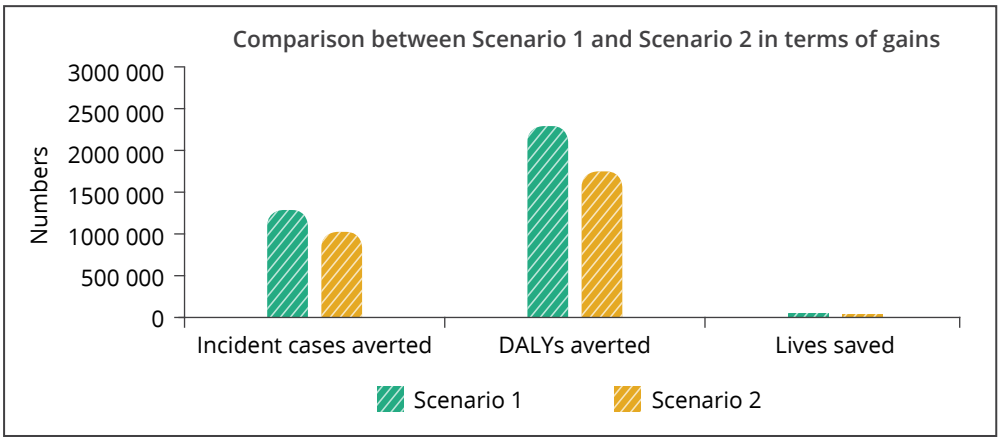
Table 1. Regional proposed targets: Scenario 1 (faster scale up over 3 years)

Coverage summary (figures in millions)								
Eligible population	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**Total**
Household contacts (including adolescents but excluding children <5 years of age)	10.77	9.99	8.72	7.42	6.32	5.45	4.82	53.49
PLHIV	2.07	1.69	1.25	0.88	0.64	0.63	0.62	7.78
Children <2 years	0.44	0.41	0.36	0.31	0.26	0.22	0.20	2.20
Children 2–5 years	0.89	0.82	0.72	0.61	0.52	0.45	0.40	4.41
Other at-risk groups	2.01	2.04	2.06	2.08	2.09	2.11	2.13	14.52
Total	**16.19**	**14.95**	**13.10**	**11.29**	**9.83**	**8.86**	**8.18**	**82.41**
Planned coverage in number	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**Total**
Isoniazid preventive treatment (IPT)	0.59	0.35	0.12	0.07	0.06	0.05	0.05	1.29
6HCP (PLHIV)	0.89	0.53	0.18	0.10	0.09	0.08	0.07	1.93
3HR (children <2 years)	0.03	0.10	0.17	0.18	0.17	0.15	0.14	0.94
3HP (adult+children 2–5 years+other risk group)	1.92	5.74	9.50	10.41	9.35	8.51	7.87	53.29
Total	**3.43**	**6.73**	**9.96**	**10.75**	**9.66**	**8.80**	**8.13**	**57.45**

Table 2. Regional targets: Scenario 2 (slower scale up over 5 years)

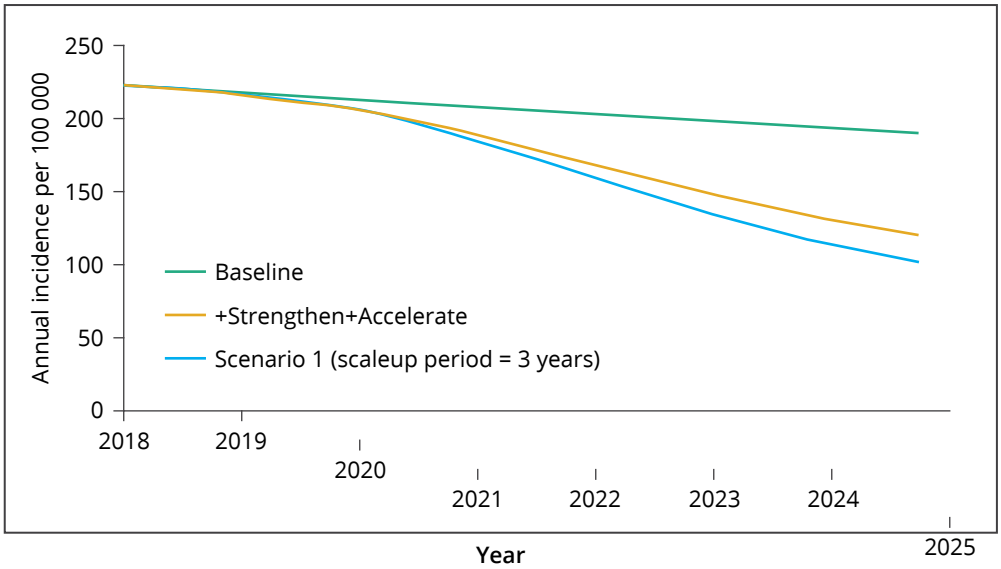
Coverage summary (figures in millions)								
Eligible population	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**Total**
Household contacts (including adolescents but excluding children <5 years of age)	10.77	9.99	8.72	7.42	6.32	5.45	4.82	53.49
PLHIV	2.07	1.69	1.25	0.88	0.64	0.63	0.62	7.78
Children <2 years	0.44	0.41	0.36	0.31	0.26	0.22	0.20	2.20
Children 2–5 years	0.89	0.82	0.72	0.61	0.52	0.45	0.40	4.41
Other at-risk groups	2.01	2.04	2.06	2.08	2.09	2.11	2.13	14.52
Total	**16.19**	**14.95**	**13.10**	**11.29**	**9.83**	**8.86**	**8.18**	**82.41**
Planned coverage in number	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**Total**
IPT	0.96	0.74	0.53	0.31	0.10	0.10	0.09	2.83
6HCP (PLHIV)	1.28	0.99	0.70	0.42	0.14	0.13	0.12	3.78
3HR (children <2 years)	0.02	0.06	0.10	0.14	0.18	0.18	0.17	0.86
3HP (adult+children 2–5 years+other risk group)	0.91	2.74	4.53	6.28	7.99	8.28	7.72	38.46
Total	**3.17**	**4.53**	**5.86**	**7.15**	**8.41**	**8.69**	**8.11**	**45.92**

Graph 5. Anticipated results in terms of incident cases averted, DALYs averted and lives saved



Decline in the regional incidence rate per 100 000 population – Assuming that TPT builds upon strengthened TB services and intensified case-finding, a total of 47% decline in incidence is expected, of which almost 15% decline will be contributed by TPT in optimistic scenario (Scenario 1) (Graph 6) and a lesser decline if there is delay in coverage (Scenario 2) (Graph 7).

Graph 6. Potential achievements in the SEA Region for declining incidence in Scenario 1



It is suggested to the countries that they should plan on priority for rapid treatment coverage of the eligible, at-risk people to make a dent on the incidence of TB. This approach would be also cost-effective with gradual anticipated decline of prices of TPT medicines over 2019–2025 in terms of reduction in costs/DALYs averted. With an anticipated massive cost reduction of new and safer drugs, preventive treatment will become highly cost-effective, with less than US$ 400 per DALY averted on average across the Region, and these costs are expected to get lower as the programmatic management of LBTI scales up.

Countries should plan on priority for rapid treatment coverage of the eligible, at risk people to make a dent on the incidence of TB.

OPERATIONAL CONSIDERATIONS

This chapter will help the countries in developing uniform understanding about how to develop their plan for programmatic management of LTBI in line with the WHO guidelines. To establish such a plan and operationalize TPT services based on that plan, countries should focus on four major areas, namely, policy, sources of funding, service delivery, and monitoring and evaluation. The discussion points and suggestions in this chapter revolve around these four areas. Advocacy being a cross-cutting theme will touch upon all the areas. Focus will also be on the role and voice of the affected and vulnerable communities, which is equally critical to influence policy and operational decisions.

IDENTIFYING AND PRIORITIZING THE ELIGIBLE POPULATION

Box 13 shows the key target groups for TPT as per the WHO guidelines and their segregated numbers that the countries should identify and treat. The country-wise and year-wise targets are given in Annexure A.

Box 13

Eligible population for TPT in countries of the SEA Region (2019)

A. Household contacts of bacteriologically confirmed index cases of TB, further segregated treatment regimen-wise, as
   - Children under 2 years
   - Children between 2 and 5 years
   - Others including adults, adolescents and children above 5 years

B. PLHIV

C. Other at-risk target population

Total estimated population

Guided by the local epidemiological situation, presence of high-risk and vulnerable groups and those exposed to occupational risks such as health workers, silicosis, etc., are considerations for selecting and prioritizing the other at-risk target populations.

It is suggested that countries can select and prioritize the other at-risk target populations according to their local epidemiological situation, presence of high-risk and vulnerable groups and those exposed to occupational risks such as health workers, silicosis, etc. However, there are low-hanging fruit for LTBI

management where no testing is needed – specifically children under 5 years who are contacts of a bacteriologically confirmed index case of TB and PLHIV. Each Member State is urged to rapidly scale up TPT among these populations. To select vulnerable groups, countries should follow the operational guidance of WHO and Stop TB Partnership (Box 14) *(22)*.

Box 14

Vulnerable groups

Type of vulnerability	Driving factor of vulnerability	Possible vulnerable groups
Clinical	Immunosuppression	PLHIV, silicosis, patients on dialysis/ anti-TNF treatment/on transplant surgery, illicit drug users, interstitial lung diseases, people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people[v]
Social and occupational	Poor living condition and exposure	Health workers, mining workers, prisoners, slum-dwellers, mobile and migratory population
Geographical	Poor access to services and information	Indigenous people, tribal populations, difficult-to-reach populations

Annexure H gives a sample of field-tested household-level vulnerability screening tool, which could be used as a reference material for the countries. The tool will help the interviewers to document the risk of TB transmission among the household members by screening them on the presence or absence of specific vulnerability factors such as past or family history of TB, diabetes, HIV, malnutrition, smoking, alcoholism, etc. The tool can be useful in determining the risk of TB at the community level and identifying the at-risk population for TB screening as well as selecting for TPT.

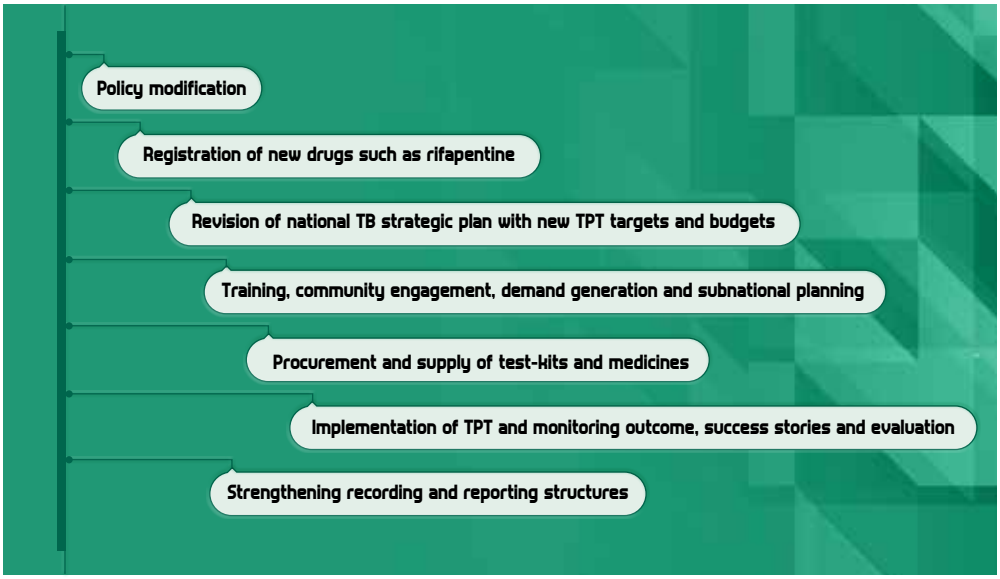
[v] WHO management guidelines on LTBI do not recommend the systematic testing of the last four groups under the clinical vulnerability category until they are linked to the recommended condition which requires testing for LTBI.

DEVELOPMENT OF COUNTRY PLANS

All Member States are encouraged to revise their national strategic plans for TB and HIV in consultation with relevant stakeholders for ensuring effective scale up of TPT. Countries need an action plan supported by updated policy guidelines. The plan should be the guiding document of the country to reach and treat the targeted eligible people with necessary logistics and trained health-care providers. The plan should articulate the funding needs, sources of funding and clear indicators to ensure monitoring of large-scale TPT services. The affected and vulnerable communities and other health, non-health and private sectors should be engaged. All-round advocacy will be crucial to bringing all relevant stakeholders including donors for a shared understanding of the plan and agreement on the high-level TPT coverage and monitoring indicators.

Diagram 2 proposes a chain of events which are necessary to happen in the country for rapid scaling up of TPT and coverage of the targeted population which is the need of the hour.

Diagram 2. Sequence of events proposed at the country level for rolling out of TPT



ADVOCACY

The NTP, along with partners and communities, is responsible for undertaking focused advocacy activities to create a supportive environment in the country for scaling up TPT, preferably with a shorter and user-friendly regimen and expand the scope of treatment among adult and adolescent household contacts and other at-risk groups based on the WHO guidelines. The advocacy initiatives should engage policy-makers and decision-makers, programme managers, health-care providers, media, CSO partners and affected communities. WHO LTBI guidelines and regional plan, 3HP study reports and success stories should act as key advocacy resources. The NTP, in coordination with the Ministry of Health (MoH), other stakeholders, CSOs and community partners should update their policies and strategic plans for a large scale and ambitious preventive treatment. Countries should explore and mobilize additional resources to augment the roll-out of the TPT action plan.

POLICY

A country with a high transmission of TB should give the same emphasis on TPT as on treatment of active TB disease. A combined implementation package of preventive and curative treatment of TB is required to generate the maximum impact on cutting transmission and reducing the pool of latent infection. This is essential to reach the desired decline rate of incidence of TB and finally the goal of ending TB in the SEA Region.

Policy adjustments to reach the targeted population with TPT services: All Member States of the SEA Region already have policies to provide TPT within their respective NTPs. An update of the existing policies will support countries to scale up their TPT services with optimum coverage of the eligible population. This, along with accelerated efforts of detection and treatment of active TB patients, will have an impact on the necessary decline of incidence of TB. It is suggested that countries should update their policy documents in accordance with the recommendations of the WHO 2018 guidelines for programmatic management of LTBI. The NTP managers should establish communication with and

coordinate advocacy efforts with the MoH, other critical stakeholders, CSO partners, health-care providers and the affected community. Table 3 suggests policy-level inclusions for countries.

Table 3. Suggested inclusions to the country-level LTBI policy guidelines

Cascade of care for programmatic management of LTBI	Existing policies of the countries on TPT *(23)*	Suggested inclusions
Identify at-risk people for LTBI testing and treatment	The following at-risk groups are recommended for TPT ⊙ Under 5 years child contacts of index patients with TB ⊙ PLHIV	Add the following at-risk groups for provision of TPT ⊙ Adult, adolescent and children above 5 years who are household contacts of index patients with TB. It is recommended to undertake a phased approach: initially focus on contacts of pulmonary TB patients and later expand to all patients with TB (including extra pulmonary TB) ⊙ Other at-risk population: as the list is exhaustive the countries should prioritize these groups in terms of local epidemiology and extent of exposure to transmission of TB
Evaluate them for active TB and rule out active TB	The eligible groups are recommended to be screened symptomatically for TB evaluation. Four-symptom screening is recommended for PLHIV.	⊙ Symptomatic screening (including four symptoms for PLHIV) should be the entry point of TB evaluation for all at-risk groups. ⊙ CXR should be preferably used when doubt prevails after symptomatic screening, especially in case of adult and adolescent household contacts (HIV-negative, >5 years). However, CXR is not a must for excluding TB. ⊙ Those with symptoms must be tested upfront via Xpert-MTB/RIF®. ⊙ Absence of TB: suggestive symptoms in an otherwise healthy and active individual are enough to be eligible for TPT.

(Continued)

(Continued)

Cascade of care for programmatic management of LTBI	Existing policies of the countries on TPT *(23)*	Suggested inclusions
Test for LTBI	⊙ No testing for LTBI is recommended for the eligible groups before initiation of TPT. ⊙ Tuberculin skin test is recommended in India for children older than 12 months living with HIV *(20)*.	Follow the WHO guidelines as follows: ⊙ LTBI testing should not be a requirement for initiating TPT for PLHIV and child household contacts under 5 years, particularly in countries with a high incidence of TB and high-transmission settings. ⊙ Either TST or IGRA can be used to test for LTBI where required. ⊙ LTBI testing and treatment for adult, adolescent and older child contacts is advised in low-incidence and low-transmission settings. ⊙ TPT can be initiated without LTBI testing for adult, adolescent and older children contacts in high-incidence settings. ⊙ For rest of the at-risk groups, testing is preferred (if available) before initiating TPT.[vi]
Initiate and provide TPT	Daily INH therapy for 6 months is recommended for TPT.	⊙ The countries should include a shorter regimen and courses of treatment such as 3HP for LTBI in their policies and guidelines. ⊙ Child contacts under 2 years should be treated with daily 3HR. ⊙ 3HP can be administered to patients receiving efavirenz and raltegravir-based ART including dolutegravir *(9)*. ⊙ 3HP should be preferably given to all eligible people who can tolerate it. Others can take 3HR or IPT.

(Continued)

[vi] Critical points to consider before formulating policies: the cut-off point between low and high incidence is still arbitrary. Moreover, any household contacts of a primary case with pulmonary TB have a similar chance of infection irrespective of the burden of the disease in the community. Hence, the chances of transmission are related more to the living conditions rather than the burden of disease.

(Continued)

Cascade of care for programmatic management of LTBI	Existing policies of the countries on TPT *(23)*	Suggested inclusions
Treatment: Monitor adverse events and treatment adherence	There is no specific recommendation on this in the current policy guidelines of the countries.	Policies such as monitoring of adverse events and treatment adherence after initiation of TPT should be included in the guidelines
Reporting of TPT	The countries currently report coverage of eligible people who are initiated on TPT.	Following elements to be included in recording and reporting systems of TPT ⊙ Coverage of eligible people who have undergone TB evaluation before TPT initiation ⊙ Occurrence of adverse events ⊙ Treatment completion

Notes: The policy guidelines and plan should promote universal health coverage and public financing for management of LTBI. Moreover, dedicated human resources and service delivery should be allocated. NTPs should have meaningful engagement with the affected communities, private sector, other relevant health programmes and line ministries in both planning and

Meeting critical operational needs at the country level

Integrated with NTP, health system and community system

– TPT should be provided to the eligible people within the same package of services of the NTP of the country using the same resources of the health system.[vii] This is the realistic, feasible and cost-effective way to scale up TPT. A recently notified TB patient and his/her household contacts including children should be regarded as the whole unit of beneficiaries of NTP where those with active disease should be initiated on ATT and rest of the eligible persons on TPT as per the guidelines. The monitoring for treatment adherence

[vii] Countries should have a plan for additional human resources to screen household contacts of notified patients with TB in case of shortage of human resource as screening of household contacts is the opening for initiating TPT. The role of CSO partners, affected communities and cured patients' groups would be vital to perform such household-level screening of household contacts together with the health staff for enhancing the coverage of TPT in countries.

can be performed together for all of them by using the same resources to ensure successful completion of ATT by the patient with TB and TPT by his/her healthy contacts. Similarly, PLHIV can have access to TPT services as part of their continuum of care at the ART centres, counselling centres and existing community-based HIV projects. The demand generation and advocacy for TPT can be integrated with the overall community engagement strategies of the NTP with active involvement of the affected community members and CSO partners. Strategic integration of the NTP with maternal and child health programmes would be equally helpful to reach the child contacts of women with TB.

Intricately linked to intensified case-finding activities such as household contact investigation – The NTPs of countries have already adopted screening of the household and close contacts of the recently notified patients with TB, especially those bacteriologically confirmed as part of the intensified case-finding activities. However, countries have the opportunity to strengthen the efforts of contact screening as per the overall needs of the End TB Strategy to reach all TB cases in the community. Studies show that the prevalence of TB among household contacts of the index patients with TB is around 3.1% ( ). Additionally, the screening activity will open the window for opportunities to identify and assess household contacts, including children for their eligibility for TPT services. The same study revealed that the prevalence of LTBI was around 52% among household contacts in low- and middle-income settings and around 28% in high-income settings. Those contacts who are without active TB disease should be put on TPT and supported for treatment adherence and completion.

Diagnostic criteria for under-5 children to exclude TB – In some settings, screening of child contacts includes TST to screen for infection and CXR to screen for TB disease. However, routine assessment of exposed contacts does not require CXR or TST. These tests have limitations and are often not readily available or possible in low- and middle-income settings. In the absence of TST or CXR, symptom-based clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. A symptom-based approach means that screening can be done by health workers at a peripheral level: access to a district-level health facility is not needed. Only symptomatic contacts may require referral to the secondary level for further assessment. Recent research

on symptom-based screening of child TB contacts indicates that this contact management strategy is safe and more feasible than diagnostic test-based contact screening in resource-limited settings. Therefore, the child contacts of an active TB case, who are healthy, thriving, playful and with no symptoms, could safely be offered TPT.

FUNDING THE PLAN

Additional funding

Countries will need additional funding to scale up their TPT services as the number of eligible people will be much higher than the current TPT targets of existing NTPs. Countries may need to identify the potential sources of funding to meet additional requirements. Funding will also be needed to transition to shorter regimens and procurement of new drugs, monitor adverse events, support treatment adherence and meet additional reporting requirements as per the WHO guidelines. While assessing the need for additional funding, all Member States are urged to consider mechanisms to procure generically manufactured drugs through voluntary or compulsory licensing, or engage in price negotiations based on large-volume procurement.

Resource mapping

Resource mapping is a useful exercise to locate potential sources of funding both at the domestic and international levels. The information gathered through resource mapping can be used during submission of funding requests of countries. For example, re-programming with the “savings or efficiency gain” of the ongoing Global Fund grants can be used to scale up TPT services among the additional targeted populations. The next cycle of the Global Fund grant, which is expected from 2020, should open opportunities for rapid scaling up of TPT. Additionally, donors (such as USAID) have expressed their interest in investing in TPT in high-burden countries. Countries may wish to explore those opportunities in partnership with communities and local CSOs. Funding sources are available for conducting small-scale feasibility studies or operational

research that can be used to test the acceptability of a shorter regimen such as 3HP among the targeted population before a full-scale roll-out, or something equally relevant in the current context such as monitoring of adverse events and treatment adherence. Such studies can enrich the experiences of a country. Countries should strongly advocate for such extra funding requirements and justify them with adequate evidence.

Countries are also encouraged to mobilize domestic funding by influencing policy-level decisions with a stronger logic of the growing need to tackle LTBI among a larger number of vulnerable people. Engagement of the corporate sector with corporate social responsibility (CSR) funding and contribution from large corporate hospitals are local-level opportunities that can expand the funding base for TPT.

Scale up of TPT services will require resource mapping as well as mobilizing domestic funding.

ORGANIZING THE RESPONSE IN DIVERSE SETTINGS

The public health system of countries generally provides treatment for TB including TPT. However, the demographic, sociocultural, economic and epidemiological diversities across countries also make the health system responses highly variable. In some countries such as Bhutan, DPR Korea and Maldives, the public health system is the sole source of treatment for patients with TB whereas in countries such as Bangladesh, India and Indonesia, a large proportion of patients with TB seek care in the private health sector as the first point of contact. Hence, the response in these countries needs

to include engagement of multiple stakeholders. Further, the response in different countries can have a different scale and timelines. Low-incidence and low-burden countries such as Maldives and Sri Lanka can gear up for a more rapid scale up of TPT whereas other countries have a major task ahead to roll out their preventive treatment on a larger scale. There are variations across countries in their existing policy guidelines for treatment of LTBI, which widen the differences in health system responses.

In such situations, it is not possible to suggest an "ideal" public health response to countries for optimum implementation of programmatic management of LTBI. Table 4 gives a feasible "response matrix" where some country-specific interventions currently in use across the Region or elsewhere are listed. Member States are invited to consider this for implementing the cascade of care for LTBI programmatic management.

The matrix may also be of assistance in helping countries to develop or revise their plan for programmatic management of LTBI.

Administration of TST *(25)*: TST, if available and indicated, should be administered by the nurse of the health facility and test reading should be interpreted by the doctor of the health facility during 48 to 72 hours of administration. A patient who does not return within 72 hours will need to be rescheduled for another skin test. A second test should be scheduled as soon as possible. There is no contraindication to repeating the TST, unless a previous TST was associated with a severe reaction. The classification of TST reaction and other information on TST is given in Annexure C.

Interferon gamma release assays (IGRAs) are whole-blood tests that can aid in diagnosing *M. tuberculosis* infection. They do not help in differentiating LTBI from TB disease. Two IGRAs have been approved and are in use: (i) QuantiFERON®-TB Gold In-Tube test (QFT-GIT); and (ii) T-SPOT®.TB test (T-Spot) *(26)*. To conduct the tests, fresh blood samples are collected in the laboratories and mixed with antigens and controls. IGRA test results should be interpreted by the doctor and the patient should be given an appointment to inform about the result. If positive, necessary arrangement for TPT should be made by the doctor.

Table 4. Expected responses of a primary care level health facility in the programmatic management of LTBI

		Cascade of care			
At-risk groups (as per the WHO guidelines)	Responsibilities of the health system	Identification of eligible population	Ruling out active TB disease and diagnosing LTBI	Initiating and provision of TPT	Treatment adherence
Household contacts	Who	⊙ Community health workers (CHWs) in the community ⊙ Nurses, laboratory technicians or medical officers (MOs) in health facilities	⊙ In the community symptomatic screening can be done by CHWs. Those positive on symptomatic screening will be sent to MO for additional tests. ⊙ MOs of health facilities screen attendees of • General outpatient department (OPD) • Chest OPD • Paediatric OPD • MCH OPD	⊙ Nurses and pharmacists of health facilities	⊙ Monitoring of adverse events (AEs) and support treatment adherence by CHWs at the households ⊙ Management of AEs by MOs at health facilities ⊙ Supporting and monitoring of treatment adherence by nurses at health facilities ⊙ Supporting treatment adherence by local nongovernmental organizations (NGOs), community-based organizations (CBOs) and affected people's networks in the communities

(Continued)

(Continued)

		Cascade of care			
At-risk groups (as per the WHO guidelines)	Responsibilities of the health system	Identification of eligible population	Ruling out active TB disease and diagnosing LTBI	Initiating and provision of TPT	Treatment adherence
	How	⊙ Screening of contacts at households ⊙ Screening of household contacts at health facilities	⊙ Symptomatic screening (key) ⊙ chest radiography (CXR) (not compulsory) ⊙ Xpert MTB/RIF (if symptomatic) ⊙ TST/interferon gamma-release assay (IGRA) (low TB transmission settings and if available)	⊙ Counselling on tuberculosis preventive treatment (TPT), AEs, adherence and completion ⊙ Dispensing drugs to the person or retaining with care-provider for daily visit and directly observed treatment (DOT)	⊙ Visits and follow-up visits to health facilities in case of AEs ⊙ Telephonic follow-up ⊙ Home visit and follow-up ⊙ Psychosocial support, counselling and retrieval of those not able to continue treatment ⊙ Video observed, family DOT, integrated counselling and testing (ICT)-based adherence support

(Continued)

(Continued)

		Cascade of care			
At-risk groups (as per the WHO guidelines)	Responsibilities of the health system	Identification of eligible population	Ruling out active TB disease and diagnosing LTBI	Initiating and provision of TPT	Treatment adherence
People living with HIV (PLHIV)	Who	⊙ Antiretroviral treatment (ART) counsellors at ART centres ⊙ Counsellor at provider-initiated counselling centre (PITC) ⊙ Opioid substitution therapy (OST) counsellors at OST centres (for injecting drug users [IDUs])	⊙ MOs of ART centres/ PITCs/OST centres	⊙ Nurses and Pharmacists at ART centres/ VCTCs/OST centres	⊙ ART counsellors at ART centres ⊙ Counsellor at the PITC, counsellors at opioid substitution therapy (OST) centres (for IDUs) ⊙ MOs (for AEs), nurses ⊙ NGOs, CBOs, affected people's networks in the communities
	How	⊙ Enrolment of ART ⊙ Post-test counselling at PITC ⊙ Initiation of OST (for IDUs)	⊙ 4-symptom screening (key) ⊙ CXR (not compulsory) ⊙ Xpert MTB/RIF (if symptomatic) ⊙ TST/IGRA (if available), though LTBI testing is not necessary for PLHIV to initiate TPT	⊙ Consent-taking ⊙ Counselling on TPT, adverse drug effects, adherence and completion ⊙ Dispensing drugs to the person or retaining with care-provider for daily visit and DOT	⊙ Visits and follow-up visits to health facilities in case of AEs ⊙ Telephonic follow-up ⊙ Home visit and follow-up ⊙ Psychosocial support, counselling and retrieval of those not able to continue treatment ⊙ Video observed, Family DOT, ICT-based adherence support

(Continued)

(Continued)

		Cascade of care			
At-risk groups (as per the WHO guidelines)	Responsibilities of the health system	Identification of eligible population	Ruling out active TB disease and diagnosing LTBI	Initiating and provision of TPT	Treatment adherence
Other at-risk groups	Who	⊙ MOs of health facilities (in various departments such as pulmonology, organ transplant, nephrology, oncology, immunology, occupational health, general health care)	⊙ MOs of health facilities	⊙ Nurses and pharmacists of health facilities	⊙ MOs (for AE), nurses at health facilities ⊙ CHWs at the households ⊙ NGOs, CBOs, people's groups or networks
	How	⊙ General health screening ⊙ Clinical and laboratory investigations	⊙ Symptomatic screening ⊙ Past and family history of TB ⊙ CXR ⊙ Xpert MTB/RIF, sputum microscopy to exclude TB if symptomatic ⊙ HIV status, diabetes ⊙ TST/IGRA, if available to diagnose LTBI where active TB disease is absent	⊙ Consent-taking ⊙ Counselling on TPT, AEs, adherence and completion ⊙ Dispensing drugs to the person or retaining with care-provider for daily visit and DOT	⊙ Identifying and linking with focal points in the national programme for arrangement of drugs or appropriate referral ⊙ Follow-up visit of patients ⊙ Telephonic follow-up ⊙ Home visit and follow-up ⊙ Engage family members

(Continued)

MONITORING OF TPT

TPT is generally recorded in the treatment registers and cards of the index patients with TB and PLHIV who are enrolled for ART. However, it gives key information mostly about the number of eligible persons put on treatment. In the current scenario, the status of completion of TPT is mostly unknown. The updated WHO guidelines emphasize on completion of TPT and its reporting. Development and adoption of ICT-enabled treatment adherence tools for TPT (the same as those for treatment of TB) should be encouraged. Updating TPT coverage and completion data in the digitalized monitoring and evaluation system where TB case notification is also digitalized should be considered by each country.

The matrix of Table 5 shows the overall information need, sources and indicators that the countries can use to revise their present recording, reporting and monitoring system for programmatic management of LTBI.

Table 5. Overall information need, data sources and indicators that are required to monitor TPT

S. no.	Information need	If currently available	Relevant indicators as per WHO guidelines	Overall data source
1	Coverage of TB evaluation of the target groups for TPT initiation	Mostly not	Proportion of children under 5 years who are household contacts of TB cases (according to national guideline) who have completed investigation for TB Proportion of eligible PLHIV enrolled in HIV care who have completed investigation for TB Proportion of eligible individuals in at-risk populations (as defined by national guidelines) tested for LTBI infection	1. For household contacts ⊙ Treatment cards of the index patients with TB ⊙ TB treatment registers of the index patients with TB ⊙ Any other (TPT register, line-listing, LTBI testing register) 2. For PLHIV enrolled in ART services ⊙ Treatment cards ⊙ Treatment registers ⊙ Any other (line-listing)

(Continued)

(Continued)

S. no.	Information need	If currently available	Relevant indicators as per WHO guidelines	Overall data source
2	Coverage of TPT initiation	Yes	Proportion of children under 5 years who are household contacts of TB cases (according to national guideline) who are eligible for TPT and have started TPT Proportion of eligible PLHIV enrolled in HIV care and started on TPT Proportion of eligible individuals in at-risk populations (as defined by national guidelines) with a positive LTBI test who are eligible for TPT and have started TPT	3. Other at-risk population Sources - according to the sites of LTBI testing and treatment ⊙ Hospital records department-wise ⊙ Treatment registers ⊙ Patient treatment cards ⊙ Pharmacy records
3	Coverage of TPT completion	Mostly not	Proportion of children under 5 years who are household contacts of TB cases (according to national guideline) who have completed a course of TPT Proportion of eligible PLHIV who completed course of TPT Proportion of eligible individuals in at-risk populations (as defined by national guidelines) with a positive LTBI test who have started TPT and completed the course	

ADHERENCE MONITORING IN TPT -GENERAL PRINCIPLES

Many variables affect a patient's adherence to LTBI treatment. Using shorter, safer treatment regimens can help the patients to complete treatment.

Barriers to adherence – factors at different levels

Clinic-related variables

- Long waiting time for appointment and referrals
- Long waiting time at health facilities
- Inconvenient facility hours

Patient-related barriers

- Misinformation or confusion about certain issues such as
  - Why should I take the medicines when I am healthy?
  - TB-related stigma, misconception, myths
  - No awareness/education on LTBI
  - The term "latent" sometimes creates confusion and fear
- Residential instability
- Lack of financial resources
- Poor access to health care
- Coexisting medical conditions
- Culture and language
- Religious practices (e.g. fasting from food)

(Continued)

(Continued)

Treatment barriers

- Complexity and duration of treatment
- Side-effects of medication
- Obtaining refills
- Frequency of clinic visits
- Cost, including insurance co-payment

Possible techniques to improve adherence to TPT

The 12-dose regimen of 3HP can be given under DOT or SAT. Health-care providers should choose the mode of administration (DOT or SAT) based on local practice, attributes and preferences of individual patients, and other considerations including risk of progression to severe forms of TB disease. However, it is important to consider supportive measures including incentives to promote adherence, more so if a longer regimen is being administered. In some situations, mobile technology may be helpful in ensuring treatment adherence. Some techniques that countries may consider for promoting treatment adherence are to

- engage communities and peer groups in counselling of the patient and contacts.
- provide thorough family education on TB and LTBI to index patients with TB and their household contacts together.
- provide treatment to household contacts together with their index patient with TB from the same facility or community-based provider.
- promote adherence using incentives.
- ensure confidentiality.
- suggest or provide patient reminders through mobile phone messages, home-visits.
- make TPT an integral part of their continuum of care for PLHIV enrolled for ART.

MONITORING AND MANAGEMENT OF ADVERSE REACTIONS

Adverse reactions of drugs pose a challenge in TB case management, so monitoring of adverse events and reporting is necessary.

It must be noted that hepatotoxicity is significantly less of a problem with 3HP than 6H or 9H *(26)*.

Potential adverse reactions of common LTBI drugs	
Isoniazid (INH)	**Rifampicin (RIF) and rifapentine (RPT)**
Clinical hepatitis occurs in about 0.1% of people taking INH and is more common when INH is combined with other hepatotoxic agents. Factors that may increase either of these rates or the severity of hepatitis include daily alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications which are metabolized in the liver.	Hepatotoxicity, skin rashes, hypersensitivity reactions, symptoms of the gastrointestinal tract, discoloration of body fluids
Peripheral neuropathy occurs in less than 0.2% of people taking INH in conventional doses. It is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure and alcoholism. Pyridoxine (vitamin B6) supplementation is recommended only in such conditions.	

Monitoring of adverse events of LTBI medicines *(7)* – general principles

Individuals receiving treatment for LTBI should be monitored routinely at monthly visits to health-care providers, at which time counselling about the disease process, rationale for taking treatment, importance of completing treatment and potential symptoms from the drugs prescribed should be reviewed. Patients receiving treatment should be advised to contact their

health-care provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health-care provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

Testing of baseline liver function is not required except, where feasible, for individuals with the following risk factors: history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age >35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, evidence-based clinical judgement is required to ensure that the benefit of TPT outweighs the risks; and they should be tested routinely at subsequent visits. Appropriate laboratory testing should also be done for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive vitamin B6 supplements when taking INH-containing regimens.

To ensure safe and efficacious treatment for LTBI, the health-care provider should periodically assess the patient's progress. The monitoring can be done by a trained community health worker, paramedical and clinical staff. This evaluation involves clinical monitoring and laboratory testing, as well as patient education.

Clinical monitoring

- All patients receiving LTBI treatment should be evaluated at least monthly for the following:
  - Adherence to the prescribed regimen
  - Signs and symptoms of TB disease
  - Adverse events (such as hepatitis)
- Patients being treated for LTBI who experience possible adverse events should be advised to stop medication and consult their health-care provider immediately.

Patient education and counselling

- Explain the disease process and rationale for medication in the absence of symptoms or radiographic abnormalities.
- Emphasize the importance of completing treatment for LTBI.
    - Discuss the possible side-effects of LTBI medications, which may include fever, unexplained anorexia, brown urine (colour of coffee or cola), icterus, rash, persistent paraesthesia of hands and feet, persistent fatigue or weakness lasting 3 or more days, abdominal tenderness, especially in right upper quadrant, easy bruising or bleeding, arthralgia, nausea, vomiting.
- Discuss the management of common side-effects and the need to report to health-care provider.

Laboratory testing

- Baseline laboratory testing (measurements of serum AST, ALT and bilirubin) is not routinely indicated for all patients at the start of LTBI treatment.
    - Laboratory testing at the start of LTBI therapy is recommended for patients with any of the following factors: liver disorders, history of liver disease (e.g. hepatitis B or C, alcoholic hepatitis or cirrhosis), regular use of alcohol, risks for chronic liver disease, HIV infection, pregnancy or the immediate postpartum period (i.e. within 3 months of delivery).
- Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions.
- After baseline testing, routine periodic retesting is recommended for persons who had abnormal initial results and other persons at risk for hepatic disease.
- At any time during treatment, whether or not the baseline tests were done, laboratory testing is recommended for patients who have symptoms suggestive of hepatitis (e.g. fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, brown urine, chills) or who have jaundice. Patients should be instructed, at the start of treatment and at each monthly visit, to stop taking treatment and to seek medical attention immediately if symptoms of hepatitis develop and not wait until the next clinic visit to stop treatment.

- It is generally recommended that medication be withheld if a patient's transaminase level exceeds three times the upper limit of normal if associated with symptoms or five times the upper limit of normal if the patient is asymptomatic.

To ensure safe and efficacious treatment for LTBI, the health-care provider should periodically assess the patient's progress. The monitoring can be done by a trained community health worker, paramedical and clinical staff.

COMMUNITY ENGAGEMENT

Community representatives are the end-users of health services. So, their participation and voice are key in the process of creating enabling environment for programmatic management of LTBI. Recent interactions with the members of the affected communities reveal their perspectives that should be considered both at the policy and operation level to ensure rapid treatment acceptance and coverage of the eligible population. Stigma linked to LTBI is a major issue, especially the term "latent" is often disliked by the community members as it gives the impression of a hidden disease like TB in an apparently healthy and normal person. Convincing healthy people to take preventive medication and complete the course is also a challenge. Moreover, community members should have access to right information on LTBI and TPT, the way they generally receive information about active TB and its treatment. LTBI should be discussed during community-level TB seminars, meetings or counselling sessions with equal importance of active TB to generate demand and promote TPT. Such approaches will improve awareness and knowledge on TB infection and its treatment.

There is an urgent need to build the necessary knowledge, acceptance and demand to scale up TPT. This is possible with strong community engagement, especially with those who are affected and vulnerable. This should be given due importance during policy update, field operation and monitoring of TPT. In the same context, the countries are encouraged to facilitate the participation of affected community members for sharing their views and perspectives during the critical decision-making processes on TPT at the country level.

Box 15

Active community engagement in TPT

Active engagement of patients with TB (both on treatment and cured) and PLHIV during the critical steps of programmatic management of LTBI starting from policy to implementation, monitoring and evaluation is encouraged.

Patients with TB while being initiated on treatment should be counselled about the risk of their household contacts, especially the children, which can arise from exposure to airborne transmission of infection. The information will help them demand screening of their household contacts and preventive treatment for them. Patients with TB and their family members should also be educated on the newer and acceptable regimens to augment demand in the community.

Cured patients with TB and their groups or networks (if available) can also function as treatment monitors of current patients with TB and their household contacts who are on preventive treatment. Countries may consider creating

Box 16

Rights of the patients with TB

Patients with TB have the right to quality diagnostic and treatment services. At the same time, they have the right to demand TB screening and preventive treatment for all their household members, including small children of their families.

such community-centric treatment support models, which are highly effective for demand creation, treatment adherence and successful completion of both curative and preventive treatment of TB.

Similarly, PLHIV should be sensitized to generating demand for services such as TB evaluation and TPT while being enrolled for ART. Networks of PLHIV should take the initiative on this through close collaboration with networks of TB activists and patients with TB. TPT should be equally promoted in the ongoing HIV projects of injecting drug users (IDUs), sex workers and other high-risk groups. The engagement of the respective community networks of drug users and sex workers will be helpful in promoting and scaling up TPT among those groups, together with their routine HIV prevention and treatment services.

Social media can be used to propagate knowledge of TB infection and its treatment using shorter regimens.

Box 17

Rights of PLHIV

Any person detected with HIV has the right to ask for a TB screening and immediate testing and treatment for LTBI, preferably with a shorter regimen, if no active TB is found.

PRIVATE HEALTH SECTOR ENGAGEMENT

In several of the high-burden and high-incidence countries of the SEA Region (Bangladesh, India, Indonesia, Myanmar and Thailand) and some relatively low-incidence countries such as Nepal, a large number of patients with TB seek treatment at private health-care facilities as the first point of contact. Countries have already initiated notification and standardized care with their private health-care system as part of countries' policies and needs. However, information regarding people receiving treatment for LTBI in the private health-care sector is not being captured.

It is suggested that countries should utilize the same platform currently developed and being mobilized for private sector engagement in TB case notification for collecting information about TPT by private physicians. This can be operationalized during field-level interactions with private physicians by NTP officials and partners. The sale records of private pharmacists can be reviewed for reaching a near-realistic estimation of people receiving TPT in the private sector. The local pharmacist association should be involved during such interventions.

The sample questionnaire in Annexure D can be used (after country-level modification if necessary) to interview private physicians on their experiences of diagnosing and providing TPT. Private physicians who can be targeted for the collection of such information would be preferably pulmonologists, medical specialists, nephrologists, oncologists, immunologists and occupational health specialists, but countries can take a final call on this according to their contexts and needs.

Interventions related to private sector engagement should be incorporated in the TPT action plan of the country if the country decides to engage the private sector.

RESEARCH

While revising their TPT policy guideline and action plan, countries should consider the scope of conducting research on TB infection and its treatment in the form of feasibility studies, operational research, knowledge, attitude practice (KAP) studies and others to gather and enrich country-level evidence. The research documents can be used during advocacy, programmatic reviews and resource mobilization.

Some of the global research priorities are as follows *(5)*:

1. Estimating risks of various infected populations for progression to active TB disease. This is crucial for determining the potential benefits of LTBI treatment and for designing appropriate public health interventions. In particular, the risk among the following groups needs to be explored – patients with diabetes, people with harmful use of alcohol, tobacco smokers, underweight people, people exposed to silica, patients receiving steroid

treatment, patients with rheumatological conditions and patients with cancer.

2. Defining the best algorithm for ruling out active TB. It is essential to exclude active TB before preventive treatment is given. Operational research may be needed to test the performance and feasibility of various algorithms, in particular, those for children and pregnant women.
3. Treatment options for LTBI. Some countries may conduct feasibility studies on roll-out of a shorter regimen for TPT. Research is also ongoing on the priority to find shorter, better-tolerated treatment regimens than those currently recommended. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people with alcohol use disorder and elderly people) are essential. In particular, more information is needed on the use of rifapentine in children under 2 years and pregnant women.
4. Risk of drug resistance following LTBI treatment. While most studies published so far have not documented any increased risk of drug resistance among those receiving TPT, it may be worthwhile to conduct programme-based surveillance systems and clinical studies to monitor the risk for bacterial resistance to the drugs used in LTBI treatment. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data.
5. Cost–effectiveness. Although a number of studies of the cost–effectiveness of TPT are available, there is a need to generate evidence on the cost–effectiveness of LTBI management stratified by population groups and type of intervention. Direct measurement of cost–effectiveness in certain settings and populations would allow extension of the LTBI strategy at the national or local levels.

ETHICAL CONSIDERATIONS *(5)*

LTBI testing and treatment raises a range of ethical issues. First, LTBI by definition is an asymptomatic state. This alters the perception of ethical obligations that would be imposed by active TB. For example, the absence of an immediate risk of transmission makes it unethical to restrict migration

Efforts must be made to ensure equity and human rights, so that the vulnerability of target groups do not preclude their access to screening and treatment.

based on the LTBI status of an individual. Second, the difficulty of accurate assessment of individual risk for the development of active TB poses a challenge to communication. Informed consent requires effective, adequate communication of the uncertainty in LTBI testing, the risk for development of active TB, possible side-effects of treatment and protective benefits. Risk and uncertainty must be communicated in a culturally and linguistically appropriate form and feedback obtained after screening programmes. Third, LTBI disproportionately affects individuals and groups that are already socially and medically vulnerable. Therefore, efforts must be made to ensure equity and human rights, so that the vulnerability of target groups do not preclude their access to screening and treatment. Any intervention for vulnerable groups should include minimization of the risk for stigmatization. Policies should be evaluated from an ethical perspective after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant.

Justin et al. in their commentary on ethical guidance for LTBI treatment explore ethical considerations for LTBI management in different contexts and risk groups *(27)*. The paper states that while traditionally provision of LTBI treatment has been emphasized only for the groups at highest risk of progression, particularly children under 5 years and PLHIV, a much larger group of people are at considerable risk of TB disease such as the adolescents who should be screened and started on preventive treatment. The paper also mentions screening of migrants specifically between high-incidence and low-incidence settings, whether it is long term or short term. LTBI treatment may be seen as a means of reducing catastrophic costs and financial burden that would occur if those with LTBI were to develop the disease.

ANNEXURES

ANNEXURE A

TARGETS: COUNTRY-WISE COMBINED TARGETS OF ELIGIBLE POPULATION

Countries of the SEA Region	2019	2020	2021	2022	2023	2024	2025
Bangladesh	241 379	300 190	410 711	525 925	645 596	768 727	808 333
Bhutan	800	985	1351	1720	2127	2533	2714
DPR Korea	70 821	85 699	114 365	142 960	172 494	202 863	210 876
India	2 199 675	2 619 029	3 435 158	4 246 003	5 096 679	6 067 084	6 404 710
Indonesia	559 908	695 990	960 013	1 223 543	1 494 328	1 773 452	1 873 840
Maldives	203	254	349	449	555	666	723
Myanmar	130 285	151 013	190 630	23 0144	273 516	326 690	348 538
Nepal	30 842	36 980	48 894	60 851	73 657	88 029	93 896
Sri Lanka	9430	11999	16909	22071	27568	33289	35905
Thailand	109 590	114 688	125 004	138 155	161 438	197 093	211 198
Timor-Leste	4751	5839	7844	9902	12 010	14 152	14 739

ANNEXURE B

THE CONCEPT BEHIND THE TREATMENT OF LTBI

Recent research has shown that human TB infection, from latent infection to active disease, exists within a continuous spectrum of metabolic bacterial activity and antagonistic immunological responses. This revised understanding leads us to propose two additional clinical states: incipient and subclinical TB. The recognition of incipient and subclinical TB, which helps divide latent and active TB along the clinical disease spectrum, provides opportunities for the development of diagnostic and therapeutic interventions to prevent progression to active TB disease and transmission of TB bacilli *(28)*.

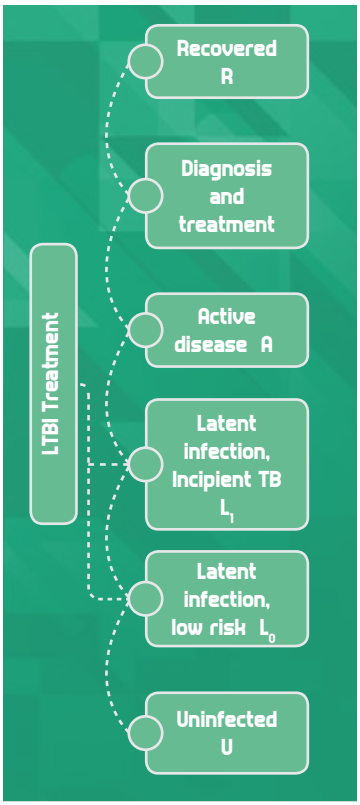
The modelling proposes using the term "incipient TB" when referring to early, contained disease in asymptomatic, relatively immunocompetent persons[viii] and using the term "subclinical TB" to refer to disease in asymptomatic, immunocompromised individuals in whom it is largely associated with loss of effective containment.[ix]

Incipient TB: Based on results from large-scale prospective studies, the term "incipient TB" is proposed to describe the constellation of upper lobe opacities over 2 cm2 in size, not attributable to another disease and occurring in an asymptomatic, apparently immunocompetent host with prior exposure to TB. It is believed that radiographically demonstrable host damage coupled with a high risk of progression distinguishes incipient TB, a very early form of disease, from LTBI. Practically speaking, identifying incipient TB as a potential forerunner of overt TB is relevant so that treatment could be deployed to prevent progression (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3192549/).

Subclinical TB: The term "subclinical TB", in association with immunosuppressed states, refers to either microbiological and/or radiographical evidence of pulmonary TB in an asymptomatic immunocompromised host. Although subclinical TB may be immunologically heterogeneous with respect to the presence of radiographical abnormalities or positive bacteriology, it represents active disease occurring in patients who are asymptomatic at the time of screening and would not be identified otherwise. Practically speaking, recognition of subclinical TB allows for the timely initiation of treatment that appears to reduce mortality (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3192549/).

Targeting and treating incipient TB is epidemiologically significant and this might be programmatically feasible to select the eligible candidate of incipient TB for TPT among "other high-risk groups" in high TB-burden settings.

Diagram 3. Basic dynamics of TB



Model

A deterministic, compartmental model capturing the TB epidemic in the SEA Region has been constructed. A representative schematic diagram of the full model is shown in Diagram 3. It is assumed, by LTBI treatment, that people move from incipient latent class to low-risk latent compartment. LTBI interventions, as per the WHO guidelines, were built upon strengthening of TB services (including private sector engagement) and intensified case-finding.

Two LTBI intervention scenarios were examined: (i) achieving the target coverage rapidly in 3 years starting from 2019; (ii) achieving the target coverage in 5 years.

ANNEXURE C

IMPORTANT CLINICAL INFORMATION ON TUBERCULIN SKIN TEST *(22)*

Reading of TST results

An induration of 5 or more millimetres is considered positive in	An induration of 10 or more millimetres is considered positive in	An induration of 15 or more millimetres is considered positive in
⊙ HIV-infected persons ⊙ A recent contact of a person with TB disease ⊙ Persons with fibrotic changes on chest radiograph consistent with prior TB ⊙ Patients with organ transplants ⊙ Persons who are immunosuppressed for other reasons	⊙ Recent immigrants (<5 years) from high-prevalence countries ⊙ Injecting drug users ⊙ Residents and employees of high-risk congregate settings ⊙ Mycobacteriology laboratory staff ⊙ Persons with clinical conditions that place them at high risk ⊙ Children under 4 years ⊙ Infants, children, and adolescents exposed to TB-affected adults in high-risk categories	Any person, including persons with no known risk factors for TB. However, targeted skin testing programmes should be conducted only among high-risk groups

False-positive and false-negative TST results

False-positive reactions: Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:	**False-negative reactions:** Some persons may not react to the TST even though they are infected with *M. tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to, the following:
⊙ Infection with non-tuberculosis mycobacteria ⊙ Previous BCG vaccination ⊙ Incorrect method of TST administration ⊙ Incorrect interpretation of reaction ⊙ Incorrect bottle of antigen used	⊙ Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system) ⊙ Recent TB infection (within 8–10 weeks of exposure) ⊙ Very old TB infection (many years) ⊙ Very young age (<6 months) ⊙ Some viral illnesses and recent live-virus vaccination (e.g. measles) ⊙ Incorrect method of TST administration ⊙ Incorrect interpretation of reaction

Repetition of TST

In general, there is no risk associated with repeated TST placements. If a person does not return within 48–72 hours for a TST reading, a second test can be placed as soon as possible. There is no contraindication to repeating the TST, unless a previous TST was associated with a severe reaction.

Boosted reaction

In some persons who are infected with *M. tuberculosis*, the ability to react to tuberculin may wane over time. When given a TST years after infection, these persons may have a false-negative reaction. However, the TST may stimulate the immune system, causing a positive, or boosted reaction to subsequent tests. Giving a second TST after an initial negative TST reaction is called two-step testing.

Two-step testing

Two-step testing is useful for the initial skin testing of adults who are going to be retested periodically, such as health-care workers or nursing home residents. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection.

ANNEXURE D

SAMPLE QUESTIONNAIRE FOR PHYSICIANS IN THE PRIVATE SECTOR TO DOCUMENT THEIR EXPERIENCES OF PROVIDING TPT

S. no.	Questions for physicians in the private sector	Tick the responses
1	Do you treat LTBI?	Yes No (If Yes go to Q. 2)
2	Whom do you treat for LTBI?	1. Household contacts of a patient with TB 2. Children (0–14) 3. Adults (14+) 4. People living with HIV (PLHIV) 5. Patients on dialysis 6. Patients who had undergone organ transplant 7. Patients with interstitial lung diseases such as silicosis 8. Any immunosuppressive patients 9. Someone with upper lobe fibrotic lesion or suggestive TB lesion in CXR without active TB 10. Someone immigrating to low-transmission countries 11. Others (specify please)

(Continued)

(Continued)

S. no.	Questions for physicians in the private sector	Tick the responses
3	What tests do you perform to diagnose LTBI?	1. CXR 2. TST/IGRA 3. Rapid molecular test or sputum microscopy to exclude TB 4. Others (specify please)
4	What treatment regimen do you use to treat LTBI?	1. INH daily monotherapy × 6 months/9 months 2. Daily INH and rifampicin × 3 months 3. Daily Rifampicin × 4 months 4. Weekly INH and rifapentine × 3 months 5. Others (specify please)

ANNEXURE E

INFORMATION ON THE AVAILABLE SHORTER REGIMEN FOR TPT

INH monotherapy has several operational challenges such as:

1. Large number of doses – the eligible person must take at least 180 doses on a daily basis for 6 months. In real-life observational studies, the treatment completion rate was found to be 40–50%.
2. A major side-effect of INH is hepatotoxicity, which increases with age and can be aggravated by pre-existing liver disease, concomitant use of other hepatotoxic medications, prior INH-related hepatotoxicity and regular alcohol consumption.
3. INH may interact with medicines such as acetaminophen, carbamazepine, ketoconazole, phenytoin and theophylline.
4. Drug stock-out of INH prophylactic medicines is not unlikely within the health system.

A more acceptable and user-friendly regimen than INH to treat LTBI would be:

1. of shorter course with lesser number of doses, which can enhance treatment completion.
2. similar or more efficacy than daily INH monotherapy.
3. well-tolerated medicine/s and fewer side-effects than INH.
4. affordable and available to the persons who need them.

The 12-dose regimen of 3HP is a combination of INH and RPT (rifapentine) given in 12 once-a-week doses. Some people refer to the 12-dose regimen of INH and RPT as "3HP".

The 12-dose regimen of INH and RPT is recommended for people 2 years of age or older, including people with HIV/AIDS who are taking antiretroviral medications that have acceptable drug–drug interactions with RPT, such as efavirenz and raltegravir including dolutegravir.

The 12-dose regimen of INH and RPT is NOT recommended for the following individuals:

- children under 2 years
- people presumed to be infected with INH or RIF-resistant *Mtb*
- pregnant women, or women expecting to become pregnant during the 12-week regimen.

The advantage of 3HP is the minimum number of doses *(12)* among other regimens, which results in higher acceptability, well-tolerated, high treatment completion rate and higher efficacy than other INH and INH–rifampicin combined regimens. 3HP is likely to be most suitable in settings of the SEA Region where the need of TPT coverage and its completion is relatively higher than that of other regions. However, due to the absence of a fixed-dose combination (FDC), a patient needs to take 7–10 pills at a time.

ANNEXURE F

SAMPLE TPT EXPANSION PLANNING TOOL FOR COUNTRIES (2019–2020)

	Target population	Baseline	Jan – Jun 2019	July – Dec 2019	Jun – Jun 2020	July – Dec 2020	TA needs
Notional Strategic plan							
Planning meeting of key stakeholders							
Founding estimates to implement new guidelines							
Guidelines update							
Technical Expert Group meeting							
Risk group identification							
Diagnostic algorithm							
Treatment guidelines							
Dissemination meeting of key stakeholders							
Expansion plan							
Coverage of PLHIV							
Coverage of child household contacts less than 5							
Coverage of household contacts then 5 years old							
Coverage of clinical risk groups							

(Continued)

(Continued)

	Target population	Baseline	Jan – Jun 2019	July – Dec 2019	Jun – Jun 2020	July – Dec 2020	TA needs
Training							
Needs assessment							
Training modules/materials							
Orientation of health staff							
Community outreach							
Mapping of community based health facilities							
Mapping of based organisations							
Plan availabilty							
Training/capacity building							
Joint activities							
Monitoring and evaluation							
Update of recording and reporting tools							
reporting data on PLHIV, child household contacts							
and other household contacts							
reporting on other clinical risk groups (Silicosis, dialysis, anti-TNF treatment, transplant)							
PSM							
Inclusion of new medicines in to the national essential medicines list (EML)							
Registration of new drugs (e.g. Rifapentine)/ Obtaining importation waiver							
Forecasting need for new drugs and supply planning							
Placement of order for new drugs (considering the need for budget and update PSM plans approvals, if required)							
Placement of order for diagnostics as per algorithm							

(Continued)

(Continued)

	Target population	Baseline	Jan – Jun 2019	July – Dec 2019	Jun – Jun 2020	July – Dec 2020	TA needs
Receiving new shipment and distribution (considering lead time of payment, manufacturing lead-time custom clearance							
Adverse drug events monitoring							
Systems for monitoring a management of adverse events							
Operational research on current coverage of TB preventive treatment and identify implementation bottlenecks (optional)							
Development of research agenda							
Protocol development							
Ethical clearance							
Conduct of research							
Adoption of research into policy							

(Continued)

ANNEXURE G

AVERAGE HOUSEHOLD SIZE AND UNDER-5 POPULATIONS COUNTRY-WISE, WHICH WERE USED FOR TARGET ESTIMATION FOR TPT

Country	Average household size (number of members)
Bangladesh	4.5
Bhutan	4.5
DPR Korea	3.9
India	4.8
Indonesia	4.0
Maldives	5.2
Myanmar	4.2
Nepal	4.4
Sri Lanka	3.8
Thailand	3.7
Timor-Leste	5.8

Source: United Nations Database of Household Size and Composition 2017 (https://www.un.org/en/development/desa/population/index.asp)

Population in the age group of 0–5 years

Country	% in 0–5 years
Bangladesh	11.32
Bhutan	10.02
DPR Korea	8.34
India	11.2
Indonesia	11.56
Maldives	12.12
Myanmar	10.1
Nepal	11.62
Sri Lanka	9.36
Thailand	6.68
Timor-Leste	20.52

Source: https://www.populationpyramid.net/

ANNEXURE H

VULNERABILITY SCREENING TOOL

Address of the household:

House no./Name: No. of household members: No. of children under 5 years: BCG scar status (Yes/ No): ~ Distance from the health post:	Phone numbers 1 2 3	**Reg. Number:** XXXX2019/ Name of the village...../ House no..... Name of the village: Name of the interviewer Name of the team leader:

Name						
Sex M/F/TG						
Age						
1a. Tribal						
1b. Coastal						
1c. Slum						
1.d H/o TB						
2a. PLHIV status						
3a. Malnutrition status (MUAC)						
3b. Past/present TB						
3c. Diabetes						
3d. COPD /asthma						
3e. Liver/ kidney disease						
3f. Bedridden/palliative care						
3g. Smoking						
3h. Alcohol						
4a. Symptoms present: – Cough – Fever – Weight loss – Haemoptysis						
4b. Sputum collected and sputum examination form filled						
Asymptomatic, but identified vulnerable requiring X-ray						

ANNEXURE I

ESTIMATION OF COST/DALY AVERTED

Estimated regimen-wise unit cost: Changes in the unit costs of different TPT regimens based on the current trend of the market prices of those medicines were anticipated. These are being called sets under eight different unit price conditions (Set 1–Set 6) and then, based on the sets year-wise total medicinal cost to meet the anticipated yearly targets of TPT were estimated, both for Scenario 1 and Scenario 2. It was also assumed in the estimation that the use of 3HP will increase with corresponding decrease of the use of rest of the regimens over time due to lesser doses and better acceptability of 3HP and chances of its availability in FDC in the near future.

Anticipated cost of various regimen

Unit cost (US$)	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6
IPT	6	6	6	6	6	6
6HCP	12	12	12	12	12	12
3HR	4	4	4	4	4	4
3HP (children)	20	17.2	14.4	11.6	8.8	6
3HP (adult)	45	39	33	27	21	15

Then for each set, the cost/DALY averted were estimated, which showed the minimum value when rapid coverage is achieved in three years and the cost of 3HP regimen coming down to US$ 15 per adult patient course and US$ 6 per child patient course.

Scenario 1: Coverage achieved in 3 years

Cost (million US$)	2019	2020	2021	2022	2023	2024	2025	Total	Cost/ DALYs averted
Set 1	13	207	405	571	526	465	417	**2603**	1089
Set 2	13	181	352	495	456	403	362	**2261**	946
Set 3	13	155	299	419	386	341	307	**1920**	803
Set 4	13	129	246	344	317	280	251	**1578**	660
Set 5	13	102	193	268	247	218	196	**1237**	517
Set 6	13	76	140	192	177	157	141	**896**	375

Scenario 2: Coverage achieved in 5 years

Cost (million US$)	2019	2020	2021	2022	2023	2024	2025	Total	Cost/ DALYs averted
Set 1	13	130	249	348	423	464	417	**2045**	1122
Set 2	13	114	217	303	367	403	362	**1779**	977
Set 3	13	99	185	257	312	341	307	**1514**	831
Set 4	13	83	154	212	256	280	251	**1248**	685
Set 5	13	67	122	166	200	218	196	**982**	539
Set 6	13	52	90	121	144	157	141	**717**	393

REFERENCES

1 Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016;13:e1002152.

2 Triasih R, Rutherford M, Lestari T, Utarini A, Robertson CF, Graham SM. Contact investigation of children exposed to tuberculosis in South East Asia: a systematic review. J Trop Med. 2012;2012:301808.

3 Zong Z, Huo F, Shi J, Jing W, Ma Y, Liang Q et al. Relapse versus reinfection of recurrent tuberculosis patients in a national tuberculosis specialized hospital in Beijing, China. Front Microbiol. 2018;9:1858.

4 Millet JP, Shaw E, Orcau A, Casals M, Miró JM, Caylà JA; Barcelona Tuberculosis Recurrence Working Group. Tuberculosis recurrence after completion treatment in a European city: reinfection or relapse? PLoS One. 2013;8:e64898.

5 Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM et al. WHO's new End TB Strategy. Lancet. 2015;385:1799–801.

6 World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva, 2018.

7 Dye C, Glaziou P, Floyd K, Raviglione M. Prospects of tuberculosis elimination. Annu Rev Public Health. 2013;34:271–86.

8 Assefa Y, Woldeyohannes S, Gelaw Y A, Hamada Y, Getahun H. Screening tools to exclude active pulmonary TB in high TB burden countries: systematic review and meta-analysis. Int J Tuberc Lung Dis. 23(6):728–734

9 Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. Atlanta: CDC; 2013 (https://www.cdc.gov/tb/publications/ltbi/pdf/targetedltbi.pdf, accessed 19 July 2019).

10 Dooley KE, Churchyard G, Savic RM, Gupte A, Marzinke MA, Zhang N et al. Safety & PK of weekly Rifapentine/Isoniazid (3HP) in adults with HIV on Dolutegravir. Conference on Retrovirus and Opportunistic Infections, 4–7 March 2019.

11 World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. WHO Guidelines approved by the Guidelines Review Committee. Geneva: World Health Organization; 2018.

12 Sandul AL, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R et al. High Rate of Treatment Completion in Program Settings with 12-Dose Weekly Isoniazid and Rifapentine (3HP) for Latent Mycobacterium tuberculosis Infection. Clin Infect Dis. 2017;65:1085–93.

13 Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015;169:247–55.

14 Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. Clin Infect Dis. 2015;61:1322–7.

15 Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155–66.

16 Doan TN, Fox GJ, Meehan MT, Scott N, Ragonnet R, Viney K et al. Cost-effectiveness of 3 months of weekly rifapentine and isoniazid compared with other standard treatment regimens for latent tuberculosis infection: a decision analysis study. J Antimicrob Chemother. 2019;74:218–27.

17 Holland DP, Sanders, GD, Hamilton CD, Stout JE. Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection. Am J Respir Crit Care Med Vol 179. pp 1055–1060, 2009

18 Huang YW, Yang SF, Yeh YP, Tsao TC, Tsao SM. Impacts of 12-dose regimen for latent tuberculosis infection: treatment completion rate and cost-effectiveness in Taiwan. Medicine (Baltimore). 2016;95:e4126.

19 Johnson KT, Churchyard GJ, David HS, Dowdy W. Cost-effectiveness of Preventive Therapy for Tuberculosis With Isoniazid and Rifapentine Versus Isoniazid Alone in High-Burden Settings. Clin Infect Dis. 2018;67:1072–78.

20 Rowe KA, Makhubele B, Hargreaves JR, Porter JD, Husler H, Pronyk PM. Adherence to TB preventive therapy for HIV positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? Int J Tuberc Lung Dis. 2005;9:263–9.

21 Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of LTBI in a clinical population in New York City. Int J Infect Dis. 2010;14:e292–7.

22 Stop TB Publications [website]. Key Population Brief for Health Workers, Key Population Brief – Indigenous People, Data for Action for TB Key, Vulnerable and Underserved Population (http://www.stoptb.org/resources/publications/, accessed 12 July 2019).

23 Jagger A, Reiter-Karam S, Hamada Y, Getahun H. National policies on the management of LTBI: review of 98 countries. Bull World Health Organ. 2018;96:173–184F.

24 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013;41:140–56.

25 Centers for Disease Control and Prevention. Fact Sheets (https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm, accessed 12 July 2019).

26 Sandul A, Nwana N, Holcombe JM, Lobato MN, Marks S, Webb R et al. High Rate of Treatment Completion in Program Settings With 12-Dose Weekly Isoniazid and Rifapentine for Latent Mycobacterium tuberculosis Infection. Clin Infect Dis. 2017;65:1085–93.

27 Denholm JT, Silva DS, Burhan E, Chaisson RE. Tuberculosis Elimination in the Asia-Pacific Region and the WHO Ethics Guidance. Trop Med Infect Dis. 2018;3(4). pii: E115.

28 Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev. 2018;31(4). pii: e00021–18.

World Health Organization
REGIONAL OFFICE FOR South-East Asia

www.searo.who.int