



REGIONAL COMMITTEE

Provisional Agenda item 8.4

*Seventy-Second Session
New Delhi
2–6 September 2019*

SEA/RC72/9

12 July 2019

Regional Action Plan on the programmatic management of latent TB Infection (LTBI) and Global Strategy for TB Research and Innovation

The WHO South-East Asia Region bears nearly half the global burden of incident tuberculosis (TB) cases. This is starkly disproportionate in relation to the population of the Region, with only about 26% of the global population living here. The current response to the TB situation in the WHO SEA Region needs to be accelerated urgently if significant progress is to be made towards achieving the End TB targets.

Accelerating efforts to End TB by 2030 is a Regional Flagship Priority of the Regional Director. To make a substantial dent in the TB epidemic, preventive treatment needs to become a key priority, in addition to accelerating TB case-finding and treatment. To align with the global commitments made at the UN High-Level Meeting on TB in September 2018 by Member States, the Region needs to reach and treat at least 10 million people with latent TB infection (LTBI) by 2022. This will require urgent and rapid scaling up of access to preventive treatment.

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

It is conservatively estimated that there are 15 million people eligible for preventive treatment in the Region as per the WHO guidelines on LTBI (as of 2018). They are those who are likely to be recently infected 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, i.e. about 270 000 fewer TB cases each year.

If the coverage of this intervention is rapidly scaled up within the next three years, it will prevent more than 1 356 569 new TB cases in the Region and avert more than 2.3 million disability-adjusted life years (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 or even less averted in individual Member States.

In addition to this Working Paper, the draft of the 'Global Strategy for TB Research and Innovation' is being attached as an information document. The Global Strategy aims to support efforts by Member States to accelerate research and innovation by setting clear objectives and priorities for advancing the science required to end TB. The document has already been put through an open consultation process inviting comments from Member States, civil society and other partners. The available comments have been duly incorporated.

The information document is being shared in line with decision WHA65(9), which stipulates "that regional committees be asked to comment on and provide inputs to all global strategies, policies and legal instruments such as conventions, regulations and codes", before it is submitted for consideration by the WHO Executive Board at its 146th session in January 2020.

The attached Working Paper was presented to the High-Level Preparatory Meeting for its review and recommendations. The HLP reviewed the paper and made the following recommendations for consideration by the Seventy-second Session of the Regional Committee:

Actions by Member States

- (1) Adapt the updated WHO guidelines as well as the Regional Action Plan on LTBI management, as appropriate, within the country context.
- (2) Prepare a fully costed national strategic plan including the revised targets for preventive treatment.
- (3) Generate demand for TB preventive treatment through advocacy with relevant stakeholders. Additionally, give adequate emphasis to co-morbidities, multisectoral engagement, social innovation and addressing migrant population.
- (4) Explore existing and potential funding opportunities to plug the resource gaps for addressing LTBI management.

Actions by WHO

- (1) Support Member States in the adaptation of Regional Action Plan, preparation and implementation of costed national strategic plans.

- (2) Support Member States in facilitating availability of newer diagnostic tools and drugs at affordable price.
- (3) Explore the possibility of submitting a regional proposal for donor agencies to support all Member States, particularly those with large funding gaps for implementing End TB strategies.
- (4) Give adequate emphasis on health system strengthening and social innovation in both the Regional Action Plan as well as the Global Strategy for TB Research and Innovation under development.

Based on the discussions at the HLP Meeting, the full document on the Regional Action Plan on the programmatic management of latent TB infection was developed, and is being attached with this Working Paper.

This Working Paper, the South-East Asia Regional Action Plan for programmatic management of latent TB infection, the draft of the 'Global Strategy for TB Research and Innovation' and the HLP Meeting recommendations are submitted to the Seventy-second Session of the WHO Regional Committee for South-East Asia for its consideration.

Introduction

1. Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinical TB disease. About one fourth of the world's population – or around 1.7 billion people – are estimated to have latent TB, which means they have been infected by TB bacteria but are not (yet) ill.
2. Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy. WHO has produced updated and consolidated guidelines for the programmatic management of LTBI in 2018, which offers 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.
3. Studies have shown that, on average, 5%–10% of those infected will develop active TB disease over the course of their lives, usually within the first five years after initial infection¹. Although early diagnosis and treatment of active TB remains the top priority, preventing TB disease and suffering by finding and treating LTBI is a fundamental step towards ending TB. Modelling of TB rates over time in high- and low-burden settings has shown that the End TB targets cannot be reached without targeted testing for and treatment of LTBI.
4. Providing preventive treatment for TB to those who are at high risk will not only decrease incident TB infections but also suffering and death, and should, therefore, be considered the standard of care. There is a global commitment to treat at least 30 million at-risk people for LTBI worldwide by 2022, which includes 4 million contacts of known TB patients who are below 5 years age, 20 million other household contacts, 6 million people living with HIV (PLHIV), and a vision to reach millions more. Member States endorsed these targets at the first ever UN High-Level Meeting on TB in New York in September 2018.
5. There is an urgent need to rapidly scale up access to testing for TB infection for high-risk populations, taking into consideration the country-wise epidemiology, and to provide for shorter TB preventive treatment, with a focus on high-burden countries.
6. 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.

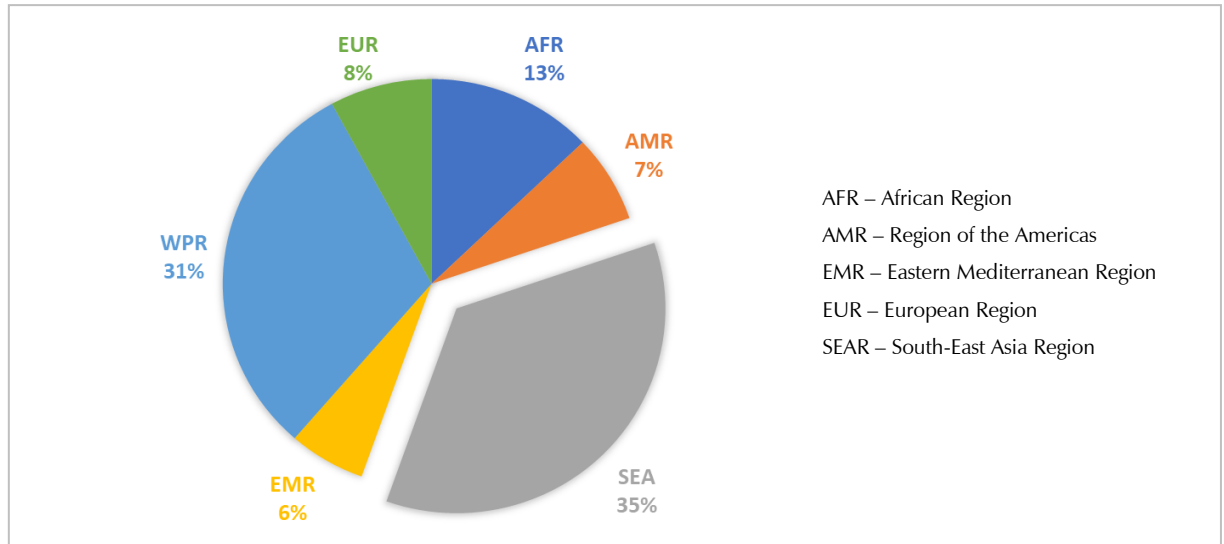
Current situation, response and challenges

7. The WHO SEA Region bears the highest TB burden globally. While the Region is home to 26% of the world's population, it is estimated that 44% of all global TB incidence and half of all TB deaths worldwide occur in this Region annually.

¹ World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva, 2018.

8. It is estimated that 587 million out of an estimated 1.7 billion people infected with TB globally live in the SEA Region and 43.3 million out of this 587 million (7%) are children below the age of 15 years². The Region accounts for around 35% of the global LTBI population (Fig. 1).

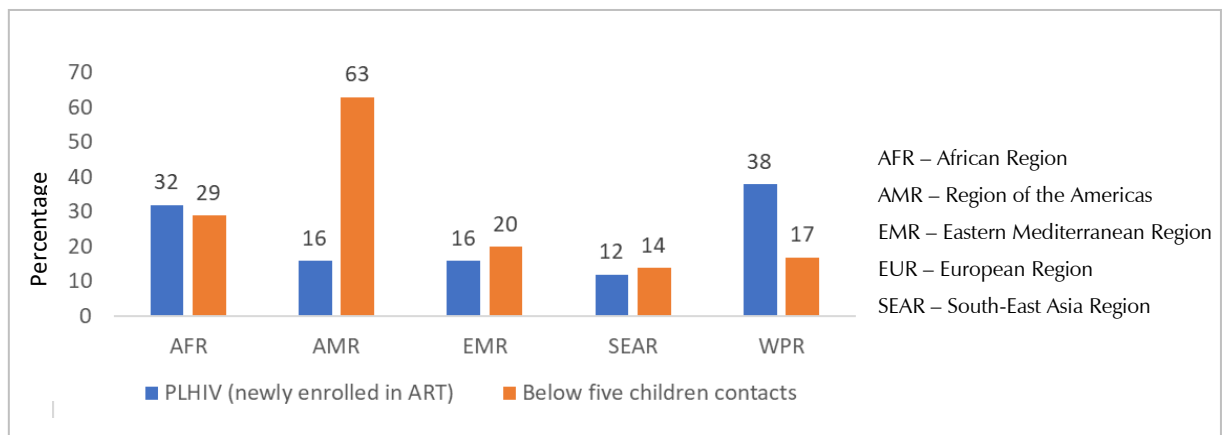
Fig. 1: The estimated proportion of people infected with TB, by WHO Region



Source : WHO Global TB report 2018

9. The SEA Region has the lowest coverage of preventive treatment among all six WHO regions, with treatment coverage at 12% among PLHIV and 14% among contacts of TB cases below 5 years of age (Fig. 2).³

Fig. 2: Coverage of TB preventive treatment by WHO Region



² Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct 25;13(10):e1002152.

³ World Health Organization. Global tuberculosis report 2018. Geneva, 2018. https://www.who.int/tb/publications/global_report/en/ - accessed 21 June 2019.

10. The Region has faced challenges to expansion of services for TB preventive treatment. However, with the recent improvements in drug regimens and a more nuanced understanding of the importance of prevention, many new opportunities have presented themselves. Some of these are discussed below.

Policy-level opportunities

- (1) The existing policy of Member States on the coverage of risk groups for preventive treatment of TB are already partially aligned with the latest WHO recommendations. With the inclusion of adult household contacts of TB patients, all Member States can become fully aligned with the new WHO guidance. All Member States already have access to daily isoniazid monotherapy for 6 months for TB preventive treatment. 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.
- (2) Demand needs to be generated for TB preventive treatment at the community level 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 opportunities

- (1) Investigation of contacts of index cases for active TB and LTBI is the backbone of case-finding activities. This also enables reaching out to people at risk of developing the disease with preventive treatment.
- (2) Specifically, for PLHIV, linkages between the HIV and TB programmes for preventive treatment can be strengthened.
- (3) Awareness and knowledge among implementers about the need for preventive treatment needs to be improved, particularly to ensure that the various new developments in treatment and diagnostics are widely understood and used.
- (4) The non-public health sector and communities offer a huge opportunity for the success of preventive treatment programmes through collaborative activities.

Monitoring opportunities

- (1) Member States currently record and report only the coverage figure of at-risk populations initiated on preventive treatment. This is segregated into household contacts below 5 years of age and PLHIV, but treatment completion is not recorded or reported. This can be amended by making small changes in the current recording and reporting formats.

The Regional Action Plan

11. The 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. Treatment for prevention of TB will accelerate the decline in incidence, prevent unnecessary suffering and reduce disability-adjusted life years (DALYs) lost. Treatment for prevention of TB is an element of the standard of care for families and close contacts of TB patients and PLHIV.

12. The Regional Plan is primarily guided by the commitments and targets of the UN High-Level Meeting on TB and WHO's updated and consolidated guidelines for the programmatic management of LTBI 2018.

13. The overall aim of the Regional Plan is to support Member States in delivering on the regional and global commitments and reaching the desired coverage of their TB preventive services.

14. The specific objectives of the Regional Plan are to:

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

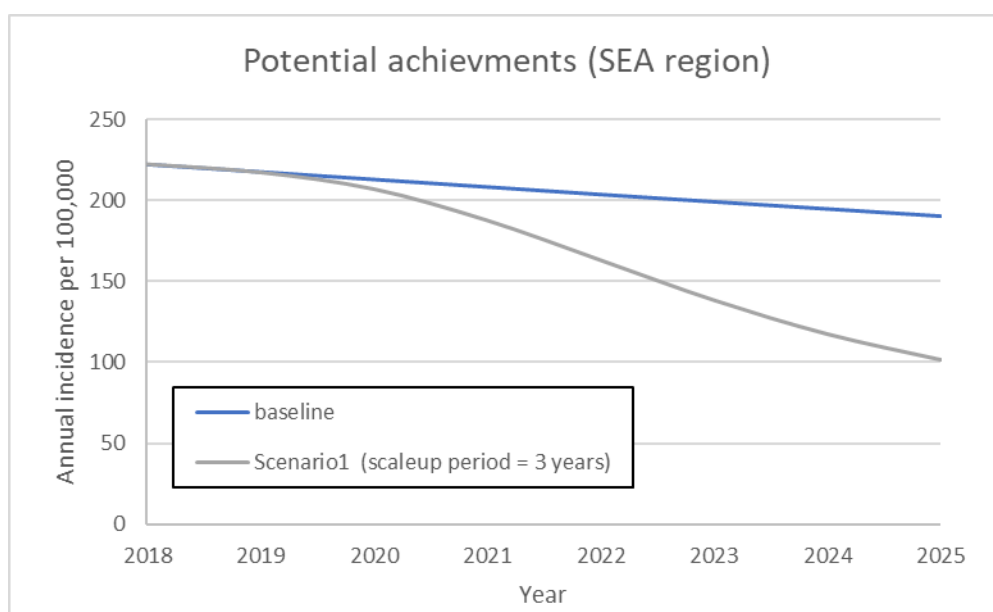
15. The Plan assumes that all countries will follow the WHO guidelines for identification of target groups – children, adolescent and adult contacts of TB cases, PLHIV and those with other immunocompromised conditions that make a person prone to the development of TB disease.

16. The Plan also assumes that preventive TB treatment is fully integrated into the national TB, HIV and maternal and child health (MCH) programmes while building on the strengths of national programmes to deliver services, and undertake active TB case-finding, specifically investigation of contacts.

17. Potential gains of TB preventive treatment in the Region: While the Regional Action Plan document describes various scenarios for coverage, in the best-case scenario, when Member States are able to reach the entire eligible population in three years, it is expected that more than 1 356 569 new TB cases will be averted by 2025, more than 2.3 million DALYs saved (Table 1) and more than 84 061 lives saved if active case-finding is implemented rapidly through contact tracing and TB preventive treatment⁴ (Fig. 3).

⁴ Modelling exercise undertaken by the WHO SEA Regional Office in 2018.

Fig. 3: The potential impact on incidence of TB of rapid scaling up of case-finding and TB preventive treatment



Source: Modelling exercise undertaken by the WHO Regional Office for SEA

Table 1: The potential impact of scaled-up case-finding and TB preventive treatment in the SEA Region

Additional total gains only because of this preventive TB treatment	2019–2025
	Complete coverage in 3 years
a. Incident cases averted	1 356 569
b. DALYs saved	2 391 132
c. Lives saved	84 061

Source: Modelling exercise undertaken by the WHO Regional Office for SEA

18. At the current prices of drugs, specifically of new drugs such as rifapentine, the total cost of treating all eligible people is expected to be around US\$ 2.6 billion from now till 2025. However, the cost of drugs is expected to come down substantially soon (generic formulations are expected later in 2019) and it is anticipated that the reduced costs could bring down the investment needs to around US\$ 800 million or less. This will bring the price down to less than US\$ 400 per DALY saved for the Region.⁵ However, Member States do not need to wait for these to become available and can progress right away by using existing formulations such as the shorter 3-month regimen with isoniazid and rifampicin (3 HR) and others.

⁵ Modelling exercise undertaken by the WHO SEA Regional Office in 2018.

The way forward

19. The way forward includes the following steps and interventions:

- Adopt the updated WHO guidelines “Latent tuberculosis infection: updated and consolidated guidelines for programmatic management” by all Member States to align country policies with the latest recommendations and also adapt the Regional Action Plan to the country contexts.
- Demand generation for TB preventive treatment through advocacy with stakeholders, civil society partners, health-care providers and affected communities. Targeted messages need to be developed for the purpose.
- Updating the national TB strategic plans in line with the revised targets of TB preventive treatment and incorporating a plan for additional resource mobilization and allocation for preventive treatment.
- Build capacity among health-care providers to implement updated LTBI guidance.
- Act swiftly to ensure access to preventive treatment by ensuring that newer, safer and shorter treatment options and diagnostics are registered and are made affordable in Member States.
- Support the process of adaptation of the Regional Action Plan by setting up a regional experts group for technical and strategic advice.

Conclusions

20. To fulfil the commitments towards ending TB, it is essential that Member States focus on treatment of LTBI and incorporate this as a priority intervention, along with strengthening of services and accelerating case detection. The Regional Action Plan on LTBI treatment provides guidance to Member States on adapting and preparing their own action plans. LTBI-related interventions should be a part of the broader national TB strategic plans. Commensurate investments will be essential to reach the targets of preventive TB treatment.

21. There is no evidence of a significant association between bacterial resistance to TB drugs and the use of isoniazid or rifamycins for the treatment of LTBI. Nonetheless, active TB disease must be excluded before TB preventive treatment is initiated, and regular follow-up is required to ensure early identification of people who develop active TB while receiving TB preventive treatment. National surveillance systems for resistance to TB drugs should be established in countries implementing programmatic management of LTBI^{6,7}.

⁶ Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis.* 2006;12(5):744–51.

⁷ den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2016;20(8):1065–71.