Report of the Global Consultation on the Programmatic Management of Latent Tuberculosis Infection

27–28 April 2016

Seoul, Republic of Korea

World Health Organization

END TB

WHO/HTM/TB/2016.08

The Global TB Programme of WHO in collaboration with the Republic of Korea's Centers for Disease Control and Prevention and International Tuberculosis Research Center organized a global consultation on the management of latent tuberculosis infection (LTBI) that was held during April 27–28, 2016, in Seoul, Republic of Korea. The objective of the meeting was to present and discuss challenges to, opportunities for, and best practices on the programmatic management of LTBI, and to consider recommendations to facilitate its implementation in both high-burden and low-burden countries.

Sustainable Development Goals in action

The meeting brought together managers of national TB programmes from both high-burden and low-burden countries, as well as researchers, technical partners, and civil society representatives. It was the first global consultation on LTBI organized in the context of The WHO End TB Strategy, and it also included representatives from resource-rich countries and those that are resource constrained. The meeting served as a platform for exchanging ideas about best practices for managing LTBI, as well as challenges and possible solutions. The issues covered included diagnosis, treatment, and programmatic management, including monitoring and evaluating LTBI. This meeting heralded a new chapter in the global response to TB by bringing together two sets of countries – those that are resource rich and have a low burden of TB and those that are resource constrained and have a high burden – and this interaction is aligned with the principles of the Sustainable Development Goals.

Managing latent TB infection: the backbone for ending TB

Overall, there was consensus that the programmatic management of LTBI should be scaled-up to achieve the targets set by The WHO End TB Strategy, including finding a path towards TB elimination. However, concern was expressed about the level of uptake of the management of LTBI and the challenges faced in scaling it up.

Although there have been efforts to scale-up the provision of isoniazid preventive therapy (IPT) among people living with HIV (PLHIV) in countries with a high burden of TB, it was noted that this has not always been the practice in countries with a low burden, often due to doubt among clinicians

about the risk of exposure and the likelihood that a person living with HIV might develop active TB. Nonetheless, ensuring ownership and leadership of IPT by national AIDS programmes has been a catalyst for scaling-up IPT among PLHIV in high-burden countries, as was recently witnessed in Kenya. Participants mentioned that misconceptions about the development of drug resistance following IPT still impede the scaling-up of IPT in many settings, although scaling-up the use of the Xpert MTB/RIF assay has helped to address such concerns by enhancing clinicians' confidence in ruling out active TB before administering IPT. Groups considered clinically at risk, such as patients initiating anti-tumour necrosis factor treatment and immigrants from countries with a high burden of TB, have been targeted for TB prevention in low-burden countries. Norway and the Netherlands have set examples by providing LTBI treatment to these groups and initiating national reporting of interventions to prevent TB. Among high-burden countries, South Africa has been targeting patients who have silicosis because of its large mining industry, in addition to child

contacts of people with TB and PLHIV. This emphasizes the need for prioritizing risk groups based on country-specific contexts in order to have the maximum impact and end the TB scourge.

Stepping-up efforts for children

The implementation of programmatic management of LTBI for child contacts of people living with TB has been weak in many high-burden settings. Among the countries participating in the meeting, in 2014 Cambodia put 2 707 child contacts on IPT and Mozambique put 17 026 child contacts on IPT; Ethiopia and Indonesia have prepared the policy environment for nationwide scale-up. Key barriers to scaling-up TB prevention among child contacts include inadequate resources and competing priorities, shortages, and a lack of commodities and paediatric formulations, as well as a lack of collaboration with parents. There was consensus on the need to engage with maternal and child health programmes to scale-up TB prevention. Participants emphasized the importance of engaging community health workers who are supporting parents with TB to increase the uptake of IPT among child contacts.

Contact investigation: the gateway to preventive treatment

Countries with a low burden of TB reported targeting contacts beyond children younger than 5 years living in the household; they additionally included adult contacts and contacts in congregate settings, such as residents of homes for the elderly. During the meeting, representatives from the Netherlands and the Republic of Korea presented national data on contact investigations. However, in other countries there are challenges to reporting these data; for example, the decentralized federal arrangement of the health system in Australia and the fact that LTBI is not a notifiable condition have resulted in the lack of a nationally standardized approach for surveillance. In Japan, although LTBI is routinely reported as a notifiable condition, national data about TB contacts are not available due to the decentralization of the management of, and data collection about, contacts by public health centres.

The extent of implementation of contact investigation in countries with a high burden of TB was generally weak, and none of the presenting countries shared their experiences.

Urgent actions to address key global bottlenecks

Participants noted that the challenges associated with scaling-up the programmatic management of LTBI were similar among countries, regardless of the TB burden or availability of resources. This reflects a fundamental gap in understanding the basics of the condition and a lack of advances in research and development. The key challenges shared among countries include shortages of commodities, such as tuberculin skin tests (TSTs), single tablets of isoniazid, and rifapentine. Other key challenges include poor client adherence due to the long duration of treatment, inadequate recording and reporting systems, as well as the unregulated engagement of the private for-profit sector.

Frequent stockouts of isoniazid and the lack of single tablets were raised as challenges in many countries, especially in those with a high TB burden. Potential reasons for these problems include an inadequate forecasting capacity, as well as increased use of the fixed-dose combination (FDC) of isoniazid and rifampicin to treat active TB. In addition, single isoniazid tablets are not available in some European countries, including the Netherlands, where isoniazid tablets are no longer manufactured. Participants urged global mechanisms, such as the Global Drug Facility, to ensure the availability of isoniazid tablets for both high-burden and low-burden countries. Participants also welcomed WHO's continuing efforts to estimate the number of child contacts

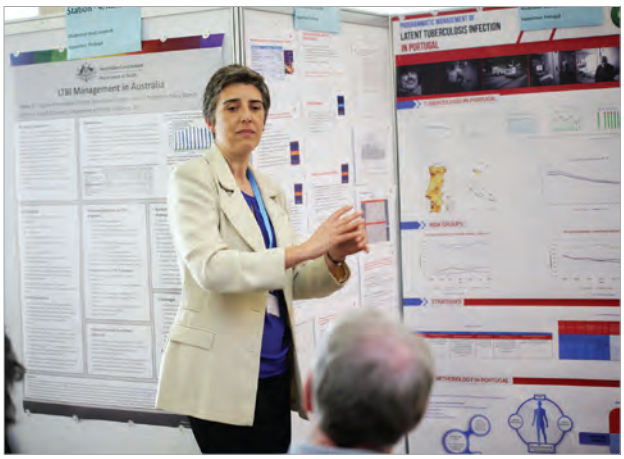

TABLE 1. **Costs to patients for managing latent tuberculosis infection (LTBI)**[a]

COUNTRY	COST TO PATIENTS WITH LATENT TUBERCULOSIS
Canada	Administration of TB programme costs varies among individual provinces and territories, but there is ultimately no cost to patients for the management of LTBI, including diagnosis and treatment
Japan	Largely free of charge; however, patients pay 5% of treatment costs
Netherlands	The cost of initial LTBI screening (for example, tuberculin skin testing during a contact investigation) is free of charge, but patients have to pay up to 385 euros per year; this cost often includes additional diagnostic costs (for example, interferon-gamma release assays) and drug costs; persons <18 years and asylum seekers are exempted
Norway	Free of charge
Republic of Korea	Costs for LTBI treatment and monitoring of side effects are free; national health insurance is applied to costs related to diagnosis, but a copayment is required
United Kingdom	Free of charge
United States of America	Costs for close contacts are free of charge and covered by local health departments; coverage for people living with HIV is usually provided by public and private insurance without out-of-pocket payments; other risk groups are covered by insurance providers (if they have insurance), and some insurance plans require copayments for diagnosis and treatment

[a] Only countries with a low burden of TB that shared information are included in the table.

eligible for preventive treatment by country, which will be pivotal to ensuring reliable forecasting. Furthermore, the wider availability of the combined rifapentine and isoniazid pill, which is under development, would also address this issue.

Participants noted with particularly grave concern that the global shortage of TSTs has been caused by the interruption of the production of purified protein derivative RT 23 SSI by the Statens Serum Institut due to privatization. This disruption may result in the circulation of TSTs with suboptimal quality, in addition to the global stockout. Participants called on the institute to address this disruption with the utmost urgency.

Additionally, costs related to the diagnosis and treatment of LTBI could be barriers to the uptake of treatment. The diagnosis and treatment of LTBI in resource-rich countries is often free for clients (**Table 1**). However, the Netherlands, a country with an excellent LTBI programme, is an outlier in which out-of-pocket costs are incurred by clients.

Access to rifapentine

Participants expressed concern about the lack of access to rifapentine in all countries, despite its inclusion in WHO's Model List of Essential Medicines since 2015. In particular, the slow registration process with the European Medicines Agency was pointed to as a key barrier blocking the wider

use of rifapentine for TB prevention in accordance with WHO's guidelines. Participants welcomed Sanofi's plans to apply for national registration in some countries before the end of 2016, including Brazil and South Africa, and called upon all national authorities to expedite the registration process in their countries. In addition, participants called for civil society organizations to generate demand and enhance their advocacy efforts to expedite the registration process, as well as to design innovative and alternative ways to improve access.

The local context is essential

Participants noted the importance of considering the local context when scaling-up LTBI management. Considerations include how to select and prioritize risk groups and how to implement locally feasible and cost-effective interventions. Participants emphasized that LTBI interventions are cost effective when compared with the cost of managing active TB disease. In fact, a systematic review conducted by WHO showed that providing LTBI management for contacts, PLHIV, and migrants from countries with a high TB burden can result in savings or in a favourable incremental cost–effectiveness ratio for the healthcare system; however, limited evidence was available for other risk groups.[1] Further studies on this topic are needed, including how to define the most appropriate cut-off for TB incidence to determine eligibility for LTBI screening among immigrants.

Should latent TB infection be a notifiable condition?

Participants noted that a critical barrier to establishing effective surveillance systems arises because LTBI is not notifiable in many countries. Additionally, monitoring and evaluation systems are often fragmented because LTBI interventions are provided throughout a wide range of clinical services, depending on the risk group. Also, there are structural and legal barriers to making LTBI notifiable. For example, in Australia several political and legal steps would need to be carried out to make it a nationally notifiable condition, and these may not be worth taking, given the magnitude of the problem. LTBI is a notifiable condition in Japan, which is why it is included in the routine surveillance system; in the Netherlands, however, although it is not a legally notifiable condition, a robust surveillance system was able to be developed.

Transformation for monitoring and evaluation

Most of the high-burden countries whose representatives attended the meeting have recording and reporting systems to measure the uptake of IPT among PLHIV. However, some participants pointed out limitations to their current systems: they capture data only from those who are newly enrolled in care. One participant also mentioned that PLHIV who initiate IPT at some point after being enrolled in care are not captured, which can lead to an underestimation of IPT coverage.

In contrast to the data on PLHIV, fewer countries had data on the uptake of IPT among child contacts. One of the barriers cited was the difficulty in collecting the denominator (the number of child contacts eligible for IPT). The existence of multiple paper-based registers was also mentioned as a barrier. The representative from Ethiopia presented a revised TB register that includes contacts to facilitate recording data about them.

Even fewer countries had data on the coverage of IPT by clinical risk group. The involvement of multiple health

[1] Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.01) (http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1, accessed 23 May 2016).

services was identified as a major challenge to obtaining these data. Norway reported the uptake of LTBI treatment among patients initiating anti-tumour necrosis factor treatment by obtaining data from multiple databases, such as the national TB register, national data on the interferon-gamma release assay, and the Norwegian prescription database.

Electronic monitoring: the shortcut to the future

The use of paper-based monitoring was cited as one of the barriers to better recording and reporting of the management of LTBI. Transitioning from paper-based registers, which often involves the use of multiple registers, to an electronic register will be helpful in implementing robust monitoring and evaluation systems for LTBI. Since 2005, the Netherlands has had a web-based register, and it has succeeded in collecting data on the coverage of LTBI treatment among different risk groups. In addition, participants suggested that in order to collect data from various risk groups, it will be important that a surveillance system has an interoperable feature, which allows data to be shared across different databases.

Engaging the private sector is crucial for managing latent TB infection

Participants agreed there is a need to engage the private sector more strongly to help scale-up the management of LTBI and implement monitoring and evaluation systems. It was pointed out that especially in low-burden countries, although contact investigation is usually conducted by public health services, care for the different clinical risk groups is managed by the private sector. For example, in the Netherlands, although LTBI is reported voluntarily, an intensified collaboration between municipal public health services and private clinicians has led to increased notification of LTBI cases diagnosed and managed in the clinical sector.[2] In the Republic of Korea, the establishment of public-private mix (PPM) network including assignment of PPM nurses in private and public hospitals has been highly effective in ensuring reporting of cases, coordinating for contact investigation and ensuring the quality of care.

Novel C-Tb skin test: hope for the future?

The suboptimal performance of diagnostic tools was raised as a challenge to diagnosing and treating LTBI. Although the TST requires less laboratory work and is cheaper than the interferon-gamma release assay, the TST can cross-react with bacille Calmette–Guérin vaccination and infection with nontuberculous mycobacteria. In addition, it is challenging to optimize diagnostic algorithms due to the varying