
27–28 April 2016
Seoul, Republic of Korea
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...
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.

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

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>COST TO PATIENTS WITH LATENT TUBERCULOSIS</th>
</tr>
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<tbody>
<tr>
<td>Canada</td>
<td>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</td>
</tr>
<tr>
<td>Japan</td>
<td>Largely free of charge; however, patients pay 5% of treatment costs</td>
</tr>
<tr>
<td>Netherlands</td>
<td>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 &lt;18 years and asylum seekers are exempted</td>
</tr>
<tr>
<td>Norway</td>
<td>Free of charge</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>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</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Free of charge</td>
</tr>
<tr>
<td>United States of America</td>
<td>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</td>
</tr>
</tbody>
</table>

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

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 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.

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
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.

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. 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.

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.

Digital healthcare was also identified as providing an opportunity for improving the management of LTBI and its monitoring and evaluation, including improving treatment adherence. Further research will be needed to assess the effectiveness of digital interventions.

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

performance of diagnostic tools depending on the immune status and vaccination history of patients. Phase III data on a novel skin test, C-Tb (Statens Serum Institut), were presented at the meeting. C-Tb uses purified ESAT-6 and CFP-10 proteins, and similar to the interferon-gamma release assay, there is no cross-reaction with bacille Calmette-Guérin or nontuberculous mycobacteria. The introduction of C-Tb will offer a significant opportunity to scale-up the management of LTBI.

UNITAID: changing the paradigm

Participants commended UNITAID for its recent identification of the treatment of LTBI in at-risk populations as one of three priority areas for intervention in TB. UNITAID’s strategy recognizes that medicines to treat LTBI and prevent progression to active TB infection could have significant impacts on the course of the epidemic, with the greatest impact occurring in populations at high risk of developing active TB (for example, PLHIV and children younger than 5 years). Further, UNITAID reiterated that shorter regimens for TB prevention may – for the first time – enable broader implementation of preventive TB therapy. Participants noted that UNITAID has the potential to change the paradigm for LTBI by addressing product-specific challenges and enabling access to novel and effective diagnosis and treatment.

Co-trimoxazole and isoniazid co-formulation

Participants pointed out the low coverage of IPT among PLHIV despite high coverage with co-trimoxazole chemoprophylaxis. The REALITY trial demonstrated the bioequivalence of an FDC of co-trimoxazole plus isoniazid plus pyridoxine compared with the drugs taken individually. The new FDC may be a significant opportunity to increase the uptake of IPT by taking advantage of the high coverage of co-trimoxazole. The FDC is undergoing WHO’s prequalification process. In addition, Sanofi is developing an FDC of rifapentine and isoniazid, which could also improve adherence to treatment by reducing the number of pills that a patient has to take.

Recommendations

The meeting made a number of recommendations to national TB programmes in high-burden and low-burden countries as well as to technical partners, both to address the challenges identified during the meeting and to scale-up the programmatic management of LTBI. The recommendations are below.

Recommendations for national TB programmes in high-burden countries

- Include in national strategic plans the scale-up of LTBI management for child contacts and PLHIV, with targets, indicators and effective systems for monitoring and evaluation.
- Engage with other relevant programmes, including in the reproductive and child health sectors, and further strengthen collaboration between TB and HIV programmes.

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Engage civil society organizations and community health workers to create demand for LTBI services, to implement LTBI testing and treatment, and to support adherence to treatment.

Engage with the private health sector to ensure the expansion of LTBI management, and ensure proper recording and reporting of implementation in both the private and public sectors.

Develop operational protocols, such as standard operating procedures and algorithms specific to each country’s context, to ensure that the scale-up of LTBI management is standardized.

Scale-up the use of the Xpert MTB/RIF assay and chest X-rays, particularly at HIV clinics, to further promote their use as diagnostic tools and enhance confidence among clinicians that active TB has been ruled out before preventive treatment is initiated.

Collaborate with national and international research centres and academics to promote research on LTBI.

Facilitate the adoption of new diagnostic tools and shorter treatment regimens, such as the rifapentine-containing regimen, as soon as they are recommended in policy.

**Recommendations for national TB programmes in low-burden countries**

- Develop a national plan for programmatic implementation of LTBI management, including prioritization of high-risk groups based on the local epidemiological and health-system contexts.
- Establish case-based and interoperable monitoring and evaluation systems to document and report on the implementation of LTBI management in all high-risk groups.

Consider making LTBI a notifiable condition by assessing national legal and policy frameworks to ensure that LTBI cases are properly documented and reported, as well as to assess the impact of programmatic implementation.

Gather information about best practices from other low-burden countries to strengthen programmatic implementation (for example, consider the electronic surveillance used in the Netherlands, the use of surveillance officers in the Republic of Korea, the cost-effectiveness analysis of screening immigrants for LTBI used in the United Kingdom).

Establish locally adapted mechanisms, including digital tools, to provide information and education both for clients and clinicians.

Provide support for patients diagnosed with and undergoing treatment for LTBI, and remove social and financial barriers, perhaps by offering public financing for LTBI management.

Engage the private health sector in managing LTBI to reach at-risk populations, especially clinical risk groups in need of LTBI treatment, and ensure there is proper recording and reporting from both the private and public sectors.

Ensure that human resources are developed and capacity is built in both the public and private sectors to promote the implementation of LTBI management.
Assess the cost effectiveness of LTBI interventions to inform policy decisions, taking into account country-specific contexts and the risk groups targeted.

Include LTBI research in national research plans; promote research on a broad range of topics, including basic, clinical, epidemiological, and operational research; and share findings nationally and globally.

Develop standard operating procedures for procuring and managing supplies of LTBI-related drugs and diagnostic tools to accurately forecast needs and prevent stockouts.

Recommendations for technical partners, including WHO and UNITAID

Support the harmonization of policy recommendations across countries, regardless of the burden of TB.

Create formal channels for communicating guidelines to national programmes as soon as they are available, and define mechanisms to monitor their implementation.

Provide technical assistance and guidance tailored to the context of a specific country, and support the development of national implementation tools.

Support the collaboration and coordination of national TB programmes with other programmes and services working with high-risk groups, including programmes for PLHIV, maternal and child health, public health and clinical service.

Provide technical assistance to ensure reliable forecasting for and quantification of commodities, including drugs and diagnostic tests.

Monitor stockouts of drugs and tests, and regularly ensure their availability by addressing key bottlenecks.

Promote the use of the combined isoniazid and co-trimoxazole co-formulation to further expand IPT in settings with a high HIV burden.

Support the registration and availability of rifapentine in countries with a high burden and those with a low burden of TB to enable the use of a shorter and once-weekly regimen.

Rapidly address the structural bottlenecks of TST stockouts and resume the production of purified protein derivative RT 23.

Global mechanisms (for example, the Global Drug Facility) should work to ensure the availability of isoniazid tablets for preventive treatment in high-burden and low-burden countries.

Ensure urgent access to and availability of the rifapentine and isoniazid combination, and assist in scaling-up LTBI treatment with this regimen.

Protect the human rights of individuals, including migrants from countries with a high burden of TB, who are diagnosed and treated for LTBI, to ensure that their rights are not infringed based on testing and diagnosis.

Promote LTBI research by developing start-up funds to attract researchers to LTBI and provide opportunities for them to interact.

Support the development of digital health tools for LTBI to facilitate the scaling-up of programmatic management.

Mobilize funds to support civil society organizations and engage them in generating demand and advocating for scaling-up LTBI management, including the development of new diagnostic tools and drugs.

Support capacity building for healthcare workers in HIV and child health programmes to increase awareness about LTBI management, eliminate misconceptions and promote their engagement in managing LTBI.

Develop implementation guidelines for LTBI to provide generic guidance – that can be adapted by countries to fit their own contexts – on programmatic implementation.
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