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

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Acknowledgements

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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BCG</td>
<td>bacille Calmette–Guérin</td>
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<td>IGRA</td>
<td>interferon-gamma release assay</td>
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<td>LTBI</td>
<td>latent tuberculosis infection</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant TB</td>
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<td>QFT</td>
<td>QuantiFERON-TB test (Qiagen)</td>
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<td>TB</td>
<td>tuberculosis</td>
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<td>TST</td>
<td>tuberculin skin test</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>USCDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The Global TB Programme of the World Health Organization (WHO) convened a technical consultation about the programmatic management of latent tuberculosis infection (LTBI) in Seoul, Republic of Korea, from 31 August to 1 September 2017. The main objective was to explore the challenges and barriers to and prospects for existing and novel LTBI diagnostics and research. The meeting was organized by WHO’s Global TB Programme in collaboration with the Korea Centers for Disease Control and Prevention and the International Tuberculosis Research Center. The consultation brought together researchers, programme managers, technical partners, manufacturers of diagnostics and donors.
Overview

Haileyesus Getahun, from WHO’s Global TB Programme, presented updates about the programmatic management of LTBI (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/hg.pdf). He highlighted the significant progress that has been made globally and the potential to expand programmatic management in the coming years, but also noted barriers to the further expansion of such programmes, including the reluctance of programme managers and health workers to provide and expand preventive treatment for TB, the difficulty of excluding active TB, concerns about the development of drug resistance, the poor adherence of clients to treatment, and the limited access to isoniazid and to testing for LTBI. He also provided information about WHO’s development of consolidated guidelines for the programmatic management of LTBI that aim to provide comprehensive and updated recommendations for managing LTBI that are relevant to all countries, regardless of their TB burden. He reiterated the importance of implementing programmatic management of LTBI and also emphasized that research to determine the best tests and treatments to use should be integral to programmatic implementation.

Target product profile for novel LTBI diagnostics

Alberto Matteelli, from the University of Brescia, presented a target product profile for a test to predict progression from TB infection to active disease (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/am.pdf). He presented an overview of current tests and emphasized the critical need for a test with improved performance to predict the progression from LTBI to the development of active TB. He discussed the developing theoretical paradigm of LTBI and highlighted the need for two complementary types of tests: tests for persistent infection and tests for incipient TB. He suggested that a test for incipient TB might allow targeting of individuals who are most at risk for developing active TB. This could pave the way for mass screening for and treatment of LTBI, which could have a significant population-level impact on reducing the incidence of TB.
C-Tb skin test

Morten Ruhwald, from the Statens Serum Institut in Denmark, presented data on the C-Tb skin test (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/mr.pdf). The C-Tb skin test uses purified ESAT-6 and CFP-10 proteins as interferon-gamma release assays (IGRAs) do, but it can be administered in the same way as the tuberculin skin test (TST). A phase III study conducted in Spain showed that the C-Tb skin test had a higher specificity than the TST and had similar performance to the QuantiFERON-TB (QFT; Qiagen) Gold In-Tube test in individuals vaccinated with bacille Calmette–Guérin (BCG). Furthermore, in a study in South Africa, the C-Tb skin test showed a significantly higher sensitivity in people living with HIV compared with the QFT Gold In-Tube test, and its performance was robust in those with CD4 cell counts ≥100 cells/mm3. He concluded by stating that the C-Tb skin test delivers performance comparable to the IGRA in the field-friendly skin test format, when using a universal cut-off of 5 mm.

DPPD skin test

Steve Reed, from the Infectious Disease Research Institute in the United States of America, presented data on the DPPD skin test (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/sr.pdf). This test uses a recombinant protein derived from a gene unique to Mycobacterium tuberculosis. The protein was shown to elicit delayed-type hypersensitivity in guinea pigs infected with M. tuberculosis but not to elicit hypersensitivity to other members of the genus. A phase II study conducted in Brazil showed it had a higher specificity than the TST in BCG-vaccinated healthy individuals. In addition, in people living with HIV, the sensitivity of the DPPD skin test was higher than that of the TST (71.1% versus 50%). In the same study, there were no reported haematomas or injection-site reactions.

Diaskintest

Yohhei Hamada, from WHO’s Global TB Programme, reviewed the literature on the performance of the Diaskintest, developed by Generium Pharmaceutical in the Russian Federation (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/yh.pdf). The Diaskintest uses the ESAT-6 and CFP-10 proteins produced by Escherichia coli BL21 (DE3)/pCFP–ESAT and, similar to the C-Tb skin test, it can be administered in the same way as the TST. The Diaskintest has been used extensively in the Russian Federation and in other countries, including Belarus, Kazakhstan, Kyrgyzstan, Turkmenistan and Ukraine. In children who have been vaccinated with BCG, it appears to have a higher specificity than the TST and similar performance to the IGRA. However, only limited data are available.

QuantiFERON-TB Gold Plus

L. Masae Kawamura, from Qiagen in the United States, presented data about the performance of QFT-Plus, the fourth generation of the QuantiFERON-TB test (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/mk.pdf). The QFT-Plus uses new antigens in addition to ESAT-6 and CFP-10, which allow measurement of CD8+ responses. A study conducted in Australia, Japan and the United States showed that QFT-Plus had a significantly higher sensitivity for active TB (94.1%) than the QFT Gold In-Tube test (89%), but maintained the specificity. Furthermore, in a study in Zambia, the sensitivity of QFT-Plus was not affected by HIV status; in another study, QFT-Plus positivity was associated with the duration and proximity of exposure to index cases. The QFT-Plus has already been approved by the U.S. Food and Drug Administration and is expected to be available in 2017.
Policy development process

Christopher Gilpin, from WHO’s Global TB Programme, gave a presentation about evaluating TB diagnostics and the process of developing policies for their use (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/cg.pdf). He also presented a framework for evaluating tests that predict progression from TB infection to active disease, emphasizing that the predictive ability and public health impact of a test are two key issues that need to be addressed when developing policies. He shared information about a recent initiative by WHO to develop an Essential Diagnostics List (http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en). Finally, he concluded by showing how WHO supports manufacturers to bring their products to market by ensuring that they are evaluated according to WHO’s requirements.

Country experiences

▶ Ethiopia

Taye Tolea Balcha, from the Armauer Hansen Research Institute, outlined the key steps that need to be taken by countries to adapt new LTBI tests to their local situations (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/tb.pdf). He stated that WHO’s endorsement of a product is an essential prerequisite for its adoption, and he emphasized that evaluating and validating the feasibility of a new technology in the local context is critical. He also highlighted the need for further research on the pathogenesis of LTBI and on its biomarkers, as well as for diagnostic tests with improved predictive performance to identify the individuals most at risk for progression to active TB disease.

▶ India

Padmapriyadarsini Chandrasekaran, from the National Institute for Research in Tuberculosis, presented information about the broad range of ongoing LTBI research activities in India (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/pc.pdf). For example, India has established a biorepository with well-characterized specimens and an associated database with standardized data, both of which can be used for future TB research (the repository and database are known as the RePort India Consortium). The repository will provide specimens to biomarker researchers in India and other countries, and this is expected to give a better understanding of the prognosis of TB disease and the pathogenesis of progression from LTBI to active disease. She also highlighted the risk factors for developing active TB, which are particularly important in India and include malnutrition, diabetes, and helminth infections, thus underlining the importance of conducting research in country-specific contexts.
Republic of Korea

Unyeong Go, from the Korea Centers for Disease Control and Prevention, stated that strong political commitment and leadership have led to intensified efforts in the Republic of Korea to address LTBI (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/ug.pdf). In 2013, the Korea TB Epidemic Investigation Service was established to support and implement contact investigation. In 2016, the Service conducted 3,502 contact investigations in congregate settings, such as schools and childcare centres. These interventions have led to a significant decline in TB notifications during the past 3 years. The country is also expanding the target groups for LTBI management and plans to screen about 1 million persons for LTBI in 2017. The key lessons learnt include the importance of understanding the need for political commitment and having a clear target for TB reduction, the importance of using a dedicated team to undertake systematic contact investigation, the need to ensure financial support for examination and treatment of LTBI, the need to engage in effective communication with the public and healthcare workers, and the need for further research and development. Participants commended the Republic of Korea for its progress and achievements in implementing programmatic management of LTBI.

South Africa

Lindiwe Mvusi, from South Africa’s National TB Control Programme, described the steps needed to adopt new diagnostic tests at the country level (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/lm.pdf). These include mobilizing financial resources; expediting regulatory approval of the test; quantifying, costing and procuring the test; developing or revising policies, standard operating procedures, and monitoring and evaluation tools; training and mentoring health workers; ensuring appropriate supplies are available and well managed; and monitoring adverse events occurring as a result of skin tests. She also emphasized that, ideally, tests should be packaged individually to avoid waste, should require minimal space for storage and should not need a cold chain.

Viet Nam

Nguyen Van Hung, from Viet Nam’s National TB Control Programme, reiterated the importance of having strong political commitment and adequate resources to enable large-scale expansion of programmatic management of LTBI, which includes implementing an effective laboratory network (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/nvh.pdf). He described an ongoing project in Viet Nam that places T-SPOT.TB tests (Oxford Immunotec) at the provincial level in addition to placing the QFT-Plus at the central level. He acknowledged the limitations of current LTBI tests and called for a test that can predict the development of active TB disease.
Optimizing the potential of novel tests

Participants acknowledged the potential of existing tests to advance programmatic management of LTBI, provided that a critical mass of evidence can be accumulated and the operational challenges can be addressed. However, it was emphasized that these considerations should not derail efforts to develop novel tests that have much better performance, particularly in predicting the progression from LTBI to active disease. Given that the benefits of preventive treatment clearly outweigh the harms, testing for LTBI is not absolutely necessary before providing preventive treatment to people living with HIV and children who are younger than 5 years old and are household contacts of someone with TB. However, testing for LTBI may be useful for other groups, such as household contacts aged 5 years and older, to identify those who would benefit most from preventive treatment. Therefore, participants called for support to optimize existing LTBI tests to enhance their utility in programmatic implementation when required. They also called for innovations to address the operational challenges associated with skin tests, such as the development of microneedles for intradermal injection, mobile applications to read reaction sizes, and a product that does not require a cold chain.

Cascade of care for managing LTBI

Richard Menzies, from McGill University in Canada, introduced the concept of addressing the cascade of care to improve programmatic implementation. This follows a review of the evidence that showed a substantial proportion of at-risk populations are lost in the cascade of care before preventive treatment is started; thus, it is critical to address bottlenecks occurring upstream of care. Results from a cluster-randomized trial of a public health intervention to enhance the investigation and treatment of contacts of active TB cases (known as ACT4) were presented. ACT4 aimed to evaluate the use of cascade analysis to identify bottlenecks and solutions for increasing the number of household contacts starting preventive TB treatment. Results from Brazil suggested that cascade analysis could significantly increase the uptake of preventive treatment by identifying barriers that had not been recognized. Participants acknowledged the value of cascade analysis to expedite the expansion of LTBI treatment and suggested that using a standardized cascade analysis approach should be explored as a component of LTBI programmatic management.

Digital health for LTBI

Zelalem Temesgen, from the Mayo Clinic in the United States, showed how digital health tools can improve the programmatic management of LTBI in various areas (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/zt.pdf), such as contact tracing, identifying the risk of reactivation, providing decision support and adherence support, and in monitoring and evaluation, as well as in education and knowledge management. For example, using digital tools such as text messaging and video-observed therapy can increase clients’ adherence to preventive treatment. Participants called for further research to examine the use of digital health solutions to enhance the programmatic management of LTBI and also for support for their implementation.
Children and adolescents

Stephen Graham, from the University of Melbourne in Australia, called for further expansion of the programmatic management of LTBI among children to reduce preventable morbidity and mortality associated with TB (http://www.who.int/entity/tb/areas-of-work/preventive-care/tbi/sg.pdf). He argued that this will require political will; decentralization and community-based integration of services; improved diagnostics; shorter, simpler and safer regimens; and effective prevention of multidrug-resistant TB (MDR-TB). He also highlighted adolescents as an important group that contributes to TB transmission in communities. Adolescents commonly develop infectious forms of TB, although this is not the case in children. Data from India and the Republic of Korea presented during the meeting also showed high LTBI prevalence rates and TB notification rates for adolescents. Participants noted that interventions to prevent TB transmission in this group need to be explored, including contact investigation and offering LTBI treatment in schools.

Shorter-course treatment

Gavin Churchyard, from the Aurum Institute in South Africa, gave an overview of ongoing research into LTBI treatment (http://www.who.int/entity/tb/areas-of-work/preventive-care/tbi/gc.pdf). Several studies are continuing to look at providing shorter courses of preventive treatment, such as 6 weeks of daily rifapentine or 4 weeks of daily rifapentine plus isoniazid. Another ongoing study in South Africa is investigating annual administration of weekly rifapentine plus isoniazid for 3 months to address the waning protection by 6 months of isoniazid monotherapy. He also presented information about a project funded by Unitaid to improve the market and public health outcomes by expanding affordable access models of short-course preventive therapy for TB (known as IMPAACT4TB). The project aims to reduce TB incidence and deaths among people living with HIV and child contacts of people with TB through sustainable implementation of the delivery of affordable, quality-assured 3-month weekly rifapentine plus isoniazid.

Financial and technical resources

Ya Diul Mukadi, from the United States Agency for International Development (USAID), stated that preventing transmission and disease progression is one of the four objectives of the United States government’s Global Tuberculosis Strategy (http://www.who.int/entity/tb/areas-of-work/preventive-care/tbi/ydm.pdf). Accordingly, the President’s Emergency Plan For AIDS Relief (known as PEPFAR) recently added a new indicator to measure completion of preventive treatment
for TB. With support from USAID, Kenya delivered preventive treatment to more than 200,000 people living with HIV as of the second quarter of 2017, and about 85% of those who started treatment, completed it.

Sara Padidar, from Unitaid, stated that Unitaid has identified TB preventive treatment in at-risk populations as one of the priority areas for intervention in TB (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/sp.pdf). Unitaid is investing US$ 59 million to catalyze access to shorter preventive treatment for high-risk groups through the IMPAACT4TB project. The project is expected to help shape the market for 3 months of weekly rifapentine plus isoniazid, which it is believed will lead to price reductions for the regimen and its global expansion beyond project countries.

Christine Ho, from the U.S. Centers for Disease Control and Prevention (USCDC), presented information about the USCDC’s efforts to expand the programmatic management of LTBI (http://www.who.int/entity/tb/areas-of-work/preventive-care/ltbi/ch.pdf). She presented a web application – the Surveillance for Tuberculosis Elimination Management System (known as STEMS) – that can be used by TB clinics to ensure optimal patient management. Furthermore, the USCDC is in the process of implementing a national TB Latent Infection Surveillance System (known as TBLISS) that is expected to be completed by 2020. Participants noted that these systems, and experiences with them, should be shared to help other countries improve their programmatic management of LTBI.

Participants acknowledged the increasing commitments and investments from donors and technical partners to expand the programmatic management of LTBI.

Priority areas for further research

During deliberations, the meeting’s participants identified the following priority areas for research.

- Understanding the epidemiology of LTBI: This could be done by including skin tests or IGRA surveys in TB prevalence surveys. Doing this would give valuable information about the burden of TB infection. Gaining a better understanding of TB transmission in communities will also be important to determining the best strategy for reducing it.

- More investment in LTBI diagnostics: This is necessary to develop a point-of-care test with improved performance to predict progression from LTBI to active TB disease. In the meantime, it would be useful to optimize the performance and utility of existing LTBI tests, such as the skin tests (C-Tb test, Diaskintest, DPPD). Furthermore, innovative methods – such as microneedles and mobile applications – need to be explored to facilitate the use of skin tests.

- Intensive treatment of LTBI in combination with active TB case finding and other interventions: This combination is important to maximize the population-level impact of reductions in TB incidence, as was observed in an early study in Alaska that provided community-wide isoniazid preventive treatment. Participants also stated that those at-risk populations for whom LTBI treatment is currently recommended only in low-burden countries (for example, clinical risk groups and immigrants) are also important groups in high-burden countries; therefore, targeting these groups in high-burden countries needs to be explored.

- Preventive treatment regimens that are more effective and safer, and shorter preventive regimens that can be used in different population groups, such as children, pregnant women and people living with HIV: These types of regimens are necessary. Furthermore, the potential of long-acting preparations – such as implants, injections and patches – also needs to be explored. Participants also emphasized the urgent need for evidence about preventive treatment for contacts of people with MDR-TB.

- Innovations in adherence support, such as using digital health solutions: These types of innovations are necessary to ensure that treatment is completed. Furthermore, participants called for larger and better surveillance systems for adverse events because the safety of treatment is critically important to getting buy-in from healthcare workers and clients.