Guidelines on the management of latent tuberculosis infection

THE END TB STRATEGY

World Health Organization

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Contents

Acknowledgements

Overall coordination and writing of the guidelines

Haileyesus Getahun and Alberto Matteelli helped coordinate the development and drafting of the guidelines, under the overall direction of Mario Raviglione.

WHO Steering Group

Dennis Falzon (Global TB Programme, WHO), Nathan Ford (HIV/AIDS Department, WHO), Haileyesus Getahun (Global TB Programme, WHO), Chris Gilpin (Global TB Programme, WHO), Christian Lienhardt (Global TB Programme, WHO), Knut Lonnroth (Global TB Programme, WHO), Alberto Matteelli (Global TB Programme, WHO), Lisa Nelson (HIV/AIDS Department, WHO), Andreas Reis (Knowledge, Ethics and Research Department, WHO), Mukund Uplekar (Global TB Programme, WHO).

Co-chairs of the WHO Guidelines Development Group

Holger Schünemann (McMaster University Health Sciences Centre, Canada); Jay Varma (US Centers for Diseases Control and Prevention, USA).

GRADE methodologist of the WHO Guidelines Development Group

Holger Schünemann (McMaster University Health Sciences Centre, Canada).

Members of WHO Guidelines Development Group

Ibrahim Abubakar (National Centre for Infectious Disease Surveillance and Control, University College London and Public Health England, London, United Kingdom of Great Britain and Northern Ireland); Draurio Barreira (National TB Programme, Ministry of Health, Brasilia, Brazil); Susana Marta Borroto Gutierrez (Pedro Kourí Institute of Tropical Medicine, La Habana, Cuba); Judith Bruchfeld (Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden); Erlina Burhan (Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia); Solange Cavalcante (Rio de Janeiro Municipal Health Secretariat FIOCRUZ, Rio de Janeiro, Brazil); Rolando Cedillos (Servicio de Infectología y Programade Atención Integral en ITS/VIH/SIDA, San Salvador, El Salvador); Cynthia Bin-Eng Chee (Tan Tock Seng Hospital, Singapore); Richard Chaisson (Center for TB Research, John Hopkins University, USA); Lucy Chesire (TB Advocacy Consortium, Nairobi, Kenya); Elizabeth Corbett (London School of Hygiene and Tropical Medicine, Blantyre, Malawi); Justin Denholm (Royal Melbourne Hospital, Melbourne, Australia); Gerard de Vries (KNCV TB Foundation, Den Haag, The Netherlands); Margaret Gale-Rowe (Public Health Agency of Canada, Ottawa, Canada); Un-Yeong Go (Department of HIV/AIDS and TB Control Korea, Korea Centers for Disease Control and Prevention, Republic of Korea); Alison Grant (London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland); Robert Horsburgh (Department of Epidemiology, Boston University School of Public Health, Boston, USA); Asker Ismayilov (Main Medical Department, Ministry of Justice, Azerbaijan); Philippe LoBue (Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, USA); Guy Marks (Woolcock Institute of Medical Research University of Sydney, Sydney, Australia); Richard Menzies (Respiratory Division, McGill University, and Montreal Chest Institute, Montreal, Canada); Giovanni Battista Migliori (WHO Collaborating Centre for TB and Lung Diseases Fondazione S. Maugeri, Tradate, Italy); Davide Mosca (Migration Health Department, International Organization of Migration, Geneva, Switzerland); Ya Diul Mukadi (Infectious Disease Division, Bureau for Global Health, US Agency for International Development, Washington, USA); Alwyn Mwinga (Zambart Project, Lusaka, Zambia); Lisa Rotz (Centers for Disease Control and Prevention, Atlanta, USA); Holger Schünemann (Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada); Surender Kumar Sharma (Department of Medicine, All India Institute of Medical Sciences,

New Delhi, India); Timothy Sterling (Vanderbilt University School of Medicine, Nashville, USA); Tamara Tayeb (National TB Programme, Ministry of Health, Riyadh, Saudi Arabia); Marieke van der Werf (European Centre for Disease Prevention and Control, Stockholm, Sweden); Wim Vandevelde (European AIDS Treatment Group, Brussels, Belgium); Jay Varma (US Centers for Diseases Control and Prevention, USA); Natalia Vezhnina (Regional Advisor on HIV/TB and Penal System Projects, Russian Federation); Constantia Voniatis (Coordinator of Clinical Laboratories, Ministry of Health, Nicosia, Cyprus); Robert John Wilkinson (Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa); Takashi Yoshiyama (Division of Respiratory Medicine, Japan Anti-Tuberculosis Association, Tokyo, Japan); Jean Pierre Zellweger (Medical Adviser, Tuberculosis Competence Centre, Berne, Switzerland).

WHO Consultants for Systematic Reviews

Saskia Den Boon (Independent consultant, United Kingdom of Great Britain and Northern Ireland); Esmee Doets (Pallas health research and consultancy BV, Rotterdam, The Netherlands); Enrico Girardi (Istituto Nazionale Malattie Infettive L. Spallanzani, Rome, Italy); Darshini Govindasamy (independent consultant, South Africa), Ross Harris (Public Health England, London, United Kingdom of Great Britain and Northern Ireland); Sandra Kik (Mc Gill University, Montreal, Canada); Katharina Kranzer (Department of Infectious Disease and Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland); Anouk Oordt-Speets (Pallas health research and consultancy BV, Rotterdam, The Netherlands); Molebogeng Rangaka (Public Health England, London, United Kingdom of Great Britain and Northern Ireland); Monica Sane Schepisi (Istituto Nazionale Malattie Infettive L. Spallanzani, Rome, Italy); Giovanni Sotgiu (Sassari University, Sassari, Italy); Helen Stagg (Public Health England, London, United Kingdom of Great Britain and Northern Ireland); Femke van Kessel (Pallas health research and consultancy BV, Rotterdam, The Netherlands); Anja van't Hoog (Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands), Marije Vonk Noordegraaf-Schouten (Pallas health research and consultancy BV, Rotterdam, The Netherlands).

Peer reviewers

Amy Bloom (US Agency for International Development (USAID), USA); Graham Bothamley (Tuberculosis Network, European Study Group Clinical trials, United Kingdom of Great Britain and Northern Ireland); Gavin Churchyard (The Aurum Institute, South Africa); Daniela Maria Cirillo (San Raffaele del Monte Tabor Foundation, San Raffaele Scientific Institute, Milan, Italy); Raquel Duarte (General Directorate of Health, Portugal); Michel Gasana (National TB Programme, Rwanda); Stephen Graham (Centre for International Child Health, Australia); Connie Erkens (KNCV Tuberculosis Foundation, The Netherlands); Brian Farrugia (Geriatric Medicine and Chest Clinic, Malta); Barbara Hauer (Robert Koch Institute, Germany); Diane Havlir (University of California, San Francisco, USA); Einar Heldal (The International Union against TB and Lung Diseases, Norway); Rein Houben (Tuberculosis Modelling and Analysis Consortium, United Kingdom of Great Britain and Northern Ireland); Mohamed Akramul Islam (BRAC Health Programme, Bangladesh); Jerker Jonsson (Swedish Institute for Infectious Disease Control, Sweden); Michael Kimerling (Bill & Melinda Gates Foundation, USA); Christopher Lange (Clinical Infectious Diseases, Medical Clinic Research Center, Borstel, Germany); Wang Lixia (National Centre for TB control and Prevention, China); Joan O'Donnell (National Disease Surveillance Unit, Ireland); Anshu Prakash (Ministry of Health and Family Welfare, India); Ejaz Qadeer (National TB Control Programme, Federal Ministry of Health, Pakistan); Lidija Ristic (Committee for TB, Ministry of Health, Serbia); Laura Sanchez-Cambronero (Ministry of Health, Social Services and Equality, Spain); Andreas Sandgren (European Centre for Disease Prevention and Control, Stockholm, Sweden); Martina Sester (Saarland University, Germany); Joseph Kimagut Sitienei (Ministry of Public Health, Kenya); Alena Skrahina (Republic Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk, Belarus); Soumya Swaminathan (National Institute for Research in Tuberculosis, Chennai, India); Ivan Solovic (National Institute for TB, Lung Diseases and Thoracic Surgery, Vysne Hagy, Slovakia); Elena Suciliene (Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, Lithuania); Maarten van Cleeff (Project Director TBCTA, KNCV Tuberculosis Foundation, The Netherlands); Francis Varaine (International Medical Co-ordinator, Médecins sans Frontières, France); Martina Vasakova (Respiratory Diseases and

Pulmonology Department at Thomayer Hospital Prague, Czech Republic); Irina Vasilyeva (Ministry of Health, Russian Federation); Mercedes Vinuesa Sebastián (Ministry of Health, Spain); Brita Askeland Winje (Norwegian Institute of Public Health, Norway); Dalene von Delft (TB PROOF, Cape Town, South Africa); Dominik Zenner (Public Health England, United Kingdom of Great Britain and Northern Ireland).

WHO Headquarters and Regional offices

Mohamed Abdel Aziz (WHO/ EMRO); Masoud Dara (WHO/EURO); Malgorzata Grzemska (WHO/ HQ); Ernesto Jaramillo (WHO/HQ); Nobuyuki Nishikiori (WHO/WPRO); Diana Weil (WHO/HQ); Karin Weyer (WHO/HQ).

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Abbreviations

GRADE	Grading of Recommendations Assessment, Development and Evaluation
IGRA	interferon-gamma release assays
LTBI	latent TB infection
MDR-TB	multidrug-resistant TB
TNF	tumour necrosis factor
TST	Mantoux tuberculin skin test

Declaration and management of conflict of interest

All the contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the Steering Group (the Legal Department of WHO was consulted when necessary) for the existence of any possible financial conflict of interest which might warrant exclusion from membership of the Guidelines Development or Peer Review Group or from the discussions as part of the guidelines development process. Intellectual conflict of interest was not considered for exclusion from membership of the Guidelines Development Group, as broader expertise on LTBI was considered as criteria for the selection. In addition, the diversity and representation in the Group was large enough to balance and overcome any potential intellectual conflict of interest. During the guidelines development process and the meeting, any emergence of intellectual conflict of interest was monitored by the Chairs and the Coordinator of the Secretariat, and any perceived intellectual conflict of interest was discussed with members of the Guidelines Development Group.

The following interests were declared:

Guidelines Development Group:

Ibrahim Abubakar declared that his employer received grants from National Institute of Health (£2.7 million for PREDICT study: Prognostic Evaluation of IGRAs and Skin test in a cohort of 10,000 contacts and migrants) and UK Department of Health (£900 000 for a randomized controlled trial to assess isoniazid-rifapentine compared to isoniazid-rifampicin on LTBI treatment completion and £490 000 for Academic, Clinical & Enterprise study, and detection of latent TB in emergency departments). He is currently the chair of the UK National Institute for Health and Care Excellence (NICE) guideline development group developing guidelines on TB which includes active and latent TB treatment. NICE pays his employer (University College of London) for his time at about £500 a day. He was a member of the European Centre for Disease Prevention and Control guideline development group on IGRAs published in 2011, for which he did not receive any remuneration. He has written extensively on this subject include a recent commentary in the Lancet on LTBI in the UK.

Cynthia Bin-Eng Chee declared that she has attended meetings pertaining to IGRAs sponsored by Qiagen (1st meeting of Asia TB experts community, Chiba, Japan 13 May 2012 and the 2nd Meeting of Asia TB Experts Community, Bangkok, Thailand, July 2013) and University of California, San Diego (3rd Global IGRA Symposium, Waikoloa, Hawaii January 2012) with estimated overall value of US$ 4500 for travel and accommodation.

Richard Chaisson declared that he received remuneration for consulting on TB drug development from Vertex of US$ 2000 in 2012 one time only and received research grants from National Institutes of Health, CDC and Gates Foundation of more than US$ 15 million which is ongoing.

Liz Corbett declared that her employer received research grants concerning the public health impact of combined TB prevention from Wellcome Trust grants.

Guy Marks declared that his employer received research grants (related to TB, though not specifically on LTBI) from National Health and Medical Research Council of Australia.

Richard Menzies declared that he received research support from Canadian Institutes of Health Research with a total grant related to latent TB infection – approximately Canadian Dollars 6 million over a 6-year period. Main research is an randomized control trial comparing 4 month-rifampicin to 9-month isoniazid for LTBI (about Canadian Dollars 1 million each year).

Surender Kumar Sharma declared that his employer received a research grant for “impact of HIV infection on latent TB among patients with HIV/TB co-infection” supported by Department of Biotechnology, Ministry of Science & Technology, Government of India (US$ 133 197.56) for which the project work is over.

Timothy Sterling declared that he received remuneration from Sanofi for a one -day consultancy meeting (and preparation) at FDA to answer questions related to the CDC-sponsored Study 26 of the TB Trials Consortium where he was the protocol chair (US$ 3800 in 2012).

Expert review Group:

Gavin Churchyard declared that he received research support grants for the following trials at the Aurum Institute: Rifaquin approximately €500 000 expired in 2011; Remox less than €200 000 which is ongoing; Thibela TB US$ 32 million expired in 2012; evaluation of Expert MTB/RIF US$ 13 million which is ongoing; evaluation of TB/HIV integration US$ 250 000 expired in 2011.

Raquel Duarte declared that she received payments from 2011 to 2014 for lectures on TB screening in patients with immune mediated inflammatory diseases candidates for biological therapy from Pfizer, Abbot and Janssen.

Diane Havlir declared that she received support grants from National Institutes of Health for research on TB.

Christopher Lange declared that he received remuneration from Celltrion Korea for consultation on the risk of TB related to treatment with bio similar TNF antagonists for one time in 2013.

Martina Sester declared that she received non-monetary support from Qiagen and Oxford Immunotech to perform investigator-initiated research studies, where the kits were in part provided free-of-charge by the two companies. She received travel support from Qiagen for presentation of the data in scientific meetings. She is a co-inventor for a patent application entitled "in vitro process for the quick determination of a patient's status relating to infection with *Mycobacterium tuberculosis*" (international patent number WO2011113953/A1).

Dalene von Delft declared that she received support for giving presentations or speeches at the UNION Conferences in 2012 and 2013 from the Treatment Action Group and USAID; support from Janssen Pharmaceuticals to attend the Leadership summit Critical Path to TB Drug Regimens; support from American Society of Tropical Medicine and Hygiene (ASTMH)-AERAS to attend meetings.

Dominik Zenner declared that he is a coauthor of one of the underpinning systematic reviews on LTBI treatment and also the head of the TB screening unit in Public Health England and has a professional interest in the subject matter.

All declarations of interest are on electronic file at the Global Tuberculosis Programme of WHO.

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Executive summary

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB. A direct measurement tool for *M. tuberculosis* infection in humans is currently unavailable. The vast majority of infected persons have no signs or symptoms of TB but are at risk for developing active tuberculosis (TB) disease. This can be averted by preventive treatment.

These *Guidelines on the management of latent tuberculosis infection* were developed in accordance to the requirements and recommended process of the WHO Guideline Review Committee, and provide public health approach guidance on evidence-based practices for testing, treating and managing LTBI in infected individuals with the highest likelihood of progression to active disease. The guidelines are also intended to provide the basis and rationale for the development of national guidelines. The guidelines are primarily targeted at high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population. Resource-limited and other middle-income countries that do not belong to the above category should implement the existing WHO guidelines on people living with HIV and child contacts below 5 years of age.

The following are the key recommendations of the guidelines:

- Systematic testing and treatment of LTBI should be performed in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. Either interferon-gamma release assays (IGRA) or Mantoux tuberculin skin test (TST) should be used to test for LTBI. *(Strong recommendation, low to very low quality of evidence)*

- Systematic testing and treatment of LTBI should be considered for prisoners, health-care workers, immigrants from high TB burden countries, homeless persons and illicit drug users. Either IGRA or TST should be used to test for LTBI. *(Conditional recommendation, low to very low quality of evidence)*

- Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers, and underweight people provided they are not already included in the above recommendations. *(Conditional recommendation, very low quality of evidence)*

- Individuals should be asked about symptoms of TB before being tested for LTBI. Chest radiography can be done if efforts are intended also for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions. *(Strong recommendation, low quality of evidence)*

- Either TST or IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000 *(Strong recommendation, low quality of evidence)*. IGRA should not replace TST in low-income and other middle-income countries. *(Strong recommendation, very low quality of evidence)*

- Treatment options recommended for LTBI include: 6-month isoniazid, or 9-month isoniazid, or 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone. *(Strong recommendation, moderate to high quality of evidence).*

In addition, the Guidelines Development Panel noted the following critical issues for consideration in the implementation of the recommendations set out in these guidelines:

- Strict clinical observation and close monitoring for the development of active TB disease among contacts of multidrug-resistant TB (MDR-TB) cases preferably for at least two years over the provision of preventive treatment. Clinicians can consider individually tailored treatment regimens based on the drug susceptibility profile of the index case, particularly for child contacts below 5 years of age, when benefits can outweigh harms with reasonable confidence.
- Regular clinical monitoring of individuals receiving treatment for latent TB through a monthly visit to the health-care provider;
- Establishment of national TB drug resistance surveillance systems while implementing national latent TB management services;
- Introduction of flexible interventions and incentives by national TB programmes that are responsive to the specific needs of population groups at risk, as well as tailored to the local context and their needs to ensure acceptable initiation of, adherence to and completion of LTBI treatment.
- Documentation of treated individuals through a functional, routine monitoring and evaluation system that is aligned with national patient monitoring and surveillance systems.
- Creation of conducive policy and programmatic environment, including the promotion of universal health coverage, development of national and local policies, standard operating procedures, as well allocation of dedicated resources.

1. Background and process

1.1. Background

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB *(1)*. One-third of the world's population is estimated to be infected with *M. tuberculosis (2)*. The vast majority of infected persons have no signs or symptoms of TB disease and are not infectious, but they are at risk for developing active TB disease and becoming infectious. The lifetime risk of reactivation TB for a person with documented LTBI is estimated to be 5–10%, with the majority developing TB disease within the first five years after initial infection *(3)*. However, the risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the host.

Reactivation TB can be averted by preventive treatment. Currently available treatments have an efficacy ranging from 60% to 90% *(4)*. The potential benefit of treatment needs to be carefully balanced against the risk of drug-related adverse events. Population-wide mass LTBI testing and treatment are not feasible due to imperfect tests, risk of serious and fatal side-effects and the high cost. The benefits are greater than the harms for infected individuals in population groups in which the risk of progression to active disease significantly exceeds that for the general population. The management of LTBI requires a comprehensive package of interventions that includes: identifying and testing those individuals who should be tested, delivering effective and safe treatment in a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and ensuring monitoring and evaluation of the process.

WHO guidelines for the management of LTBI are currently only available for people living with HIV *(5)* and for children below 5 years of age who are household contacts of TB cases *(6)*. Several WHO Member States had requested WHO for clear policy guidance on the management of LTBI, with due consideration to testing and treatment options. In addition, guidelines on the management of LTBI would be one of the necessary tools for facilitating the implementation of the Global TB Strategy after 2015 to achieve its ambitious targets of 90% reduction in TB incidence and 95% reduction in TB deaths that was endorsed by the World Health Assembly in May 2014.

With the present guidelines, WHO intends to provide guidance on how to identify and prioritize at-risk population groups who would benefit from LTBI testing and treatment and recommend diagnostic and treatment approaches with due consideration to ethical requirements.

1.2. Scope of the guidelines

The overall objective of the guidelines is to provide public health approach guidance on evidence-based practices for testing, treating and managing LTBI in individuals with the highest risk of progression to active disease. The guidelines are expected to provide the basis and rationale for the development of national guidelines for LTBI management based on available resources, epidemiology of TB including intensity of transmission, the health-care delivery system of the country, and other national and local determinants. The specific objectives of the guidelines include identifying and prioritizing at-risk population groups for targeted intervention of LTBI testing and treatment, including defining an algorithm and recommending specific treatment options.

1.3. Target audience

The proposed guidelines are, in principle, intended to benefit all WHO Member States regardless of their epidemiology of TB as the intent is to improve the diagnosis and management of LTBI in population groups with the highest likelihood of progression to active disease. However, the guidelines are primarily targeted at high-income or upper middle-income countries with an estimated

TB incidence rate of less than 100 per 100 000 population. The Panel judged that these countries are most likely to benefit from the guidelines due to their current TB epidemiology and resource availability (Annex 1). Additionally, LTBI management in high-risk groups is one of the priority actions for a TB elimination strategy in low-incidence countries, which is part of the Global End TB Strategy after 2015. Resource-limited countries and other middle-income countries that do not belong to the above category should implement existing WHO guidelines on people living with HIV *(5)* and child contacts below 5 years of age *(6)* as a priority.

National TB control programmes or their equivalents in the ministries of health are the primary target audience for these guidelines. However, the guidelines is also aimed at policy makers in other line ministries working in the areas of health, prison services, social services or immigration (such as ministries of justice or correctional services; ministries dealing with immigration).

1.4. Development of the guidelines

As part of the WHO Guideline Review Committee recommended process *(7)*, three groups were established to develop the guidelines:

1. The WHO Guideline Steering Group chaired by the Global TB Programme and involving departments of HIV/AIDS and Knowledge, Ethics and Research to lead the guideline development process;
2. The Guidelines Development Group (which is known as the Panel hereafter) composed of external content experts, national TB programme managers, academicians and representatives of patients groups and civil society, to provide inputs throughout all stages of the guideline development process. Members of the Panel were selected on the basis of balancing diversity, relevant expertise, and geographic and gender representativeness of both stakeholders and patient groups; and
3. The External Review Group composed of individuals interested in latent TB content to review the draft of the guidelines.

The Steering Group identified key questions and a comprehensive list of systematic reviews required to formulate the recommendations. It also developed the scoping document for the development of the guidelines. The Panel reviewed the scoping document and agreed with the Steering Group on the scope of the guidelines as well as key questions and outcomes to guide the systematic reviews.

The following seven key questions were identified:

1. Which populations will benefit most from LTBI diagnosis and treatment?
2. What is the most appropriate algorithm to identify individuals to be treated for LTBI?
3. What is the best treatment option for LTBI?
4. In individuals receiving treatment for LTBI, what are the best ways to monitor and manage hepatic toxicity and other adverse events?
5. What interventions are effective to improve initiation, adherence and completion of LTBI treatment?
6. Should preventive therapy be recommended for contacts of patients with multidrug-resistant TB (MDR-TB)?
7. Is the treatment and management of LTBI cost effective?

A list of potential outcomes of interest for each question was circulated to all members of the Panel and each member scored the importance of each outcome on a scale of 1 to 9 as below:

- 1 to 3 to indicate an outcome considered not important
- 4 to 6 to indicate an outcome considered important
- 7 to 9 to indicate an outcome considered critical.

The average of the scores for each outcome was used to inform the decision making.

A total of 14 systematic reviews informed this guideline development process. The Panel met in person, and communicated by conference call and email correspondence. Meetings were co-chaired by a technical expert and a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist. Recommendations were drafted taking into consideration the benefits and harms profile, costs, feasibility, acceptability, and values and preferences of clients and health-care providers. Recommendations and their relative strength were determined by consensus, and when a consensus could not be reached open voting was used to arrive at a decision. Consensus was defined as unanimous or majority agreement. Relevant recommendations from existing and valid WHO guidelines were included in the final guidelines document as deemed necessary *(5,6,8)*. Additional inputs from the Expert Review Group were also obtained. All remarks made by the Expert Review Group members were evaluated by the WHO Steering Group and considered for incorporation into the final Guidelines version.

1.5. Quality of evidence and strength of the recommendations

The quality of evidence and strength of the recommendations were assessed using the GRADE methodology whenever possible *(9)*. In the GRADE process, the quality of a body of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The usefulness of an estimate of the effect (of the intervention) depends on the level of confidence in that estimate. The higher the quality of evidence, the more likely a strong recommendation can be made; however, the decision regarding the strength of the evidence also depends on other factors.

The strength of the recommendations reflects the degree of confidence of the Panel that the desirable effects of the recommendations outweigh the undesirable effects. The desirable effects considered included beneficial health outcomes (e.g. prevention and early diagnosis of TB, reduced TB-related morbidity and mortality), less burden and more savings; whereas undesirable effects included harms, more burden and more costs. Burdens considered included the demands of adhering to the recommendations that programmes, patients or caregivers (e.g. family) may have to bear, such as having to undergo more frequent tests, taking additional medications or opting for a treatment that has a risk for toxicity.

The following levels of assessment of the evidence were used in the GRADE profiles:

Evidence level	Rationale
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect.
Low	Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

The recommendations in these guidelines were graded into two categories as follows:

1. A **strong recommendation** is one for which the Panel was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This could be either in favour of or against an intervention.
2. A **conditional recommendation** is one for which the Panel concluded that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the Panel was not confident about these trade-offs. Reasons for not being confident included: absence of high-quality evidence (data to support the recommendation are scant); presence of imprecise estimates of benefits or harms (new evidence may result in changing the balance of risk to benefit); uncertainty or variation regarding how different individuals value the outcomes (only applicable to a specific group, population or setting); small benefits and benefits that may not be worth the costs (including the costs of implementing the recommendation).

2. Recommendations

The Panel issued recommendations on the identification of individuals for latent TB testing and treatment, the algorithmic approach to test and treat LTBI, and the treatment options. The recommendations of the Panel were mainly based on critical appraisal of the evidence, the balance of anticipated benefits and harms, the values and preferences of clients and health-care providers as well as resource implications.

The overall logical approach conformed to the Panel for the development of the guidelines and the formulation of the recommendations was as follows: (1) identification of the risk groups that are eligible for treatment of latent TB infection (recommendation in section 2.1, page 13); followed by (2) evaluation of the accuracy and drawbacks of the screening tests (recommendation in section 2.2, page 15); and (3) evaluation of the effectiveness and harms of the treatment regimens to prevent progression (recommendation in section 2.3, page 18).

2.1. Identification of at-risk populations for LTBI testing and treatment

In high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000 population

- Systematic testing and treatment of LTBI should be performed in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation and patients with silicosis. Either interferon-gamma release assays (IGRA) or Mantoux tuberculin skin test (TST) should be used to test for LTBI. *(Strong recommendation, low to very low quality of evidence)*
- Systematic testing and treatment of LTBI should be considered for prisoners, health workers, immigrants from high TB burden countries, homeless persons and illicit drug users. Either IGRA or TST should be used to test for LTBI. *(Conditional recommendation, low to very low quality of evidence)*
- Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers, and underweight people unless they are already included in the above recommendations. *(Conditional recommendation, very low quality of evidence)*

For resource-limited countries and other middle-income countries that do not belong to the above category (according to existing and valid WHO guidelines) *(5,6)*:

- People living with HIV and children below 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB but have LTBI should be treated. *(Strong recommendation, high quality of evidence)*

Remarks: *Testing and treatment of LTBI should adhere to strict human rights and the highest ethical considerations. For example, positive test results or status of treatment for LTBI should not affect a person's immigration status or delay the ability to immigrate. For people living with HIV and child contacts below 5 years of age, the existing WHO guidelines should be consulted (5,6).*

The rationale for the Panel to make strong recommendations despite low to very low quality of evidence was based on its strong judgment on the increased likelihood of progression to active TB disease and the benefits of treatment outweighing the potential harms in the identified at-risk population groups. Similarly, the Panel made its conditional recommendations primarily because of the weak quality of the evidence and implementation considerations.

2.1.1. Summary of the evidence

Three systematic reviews were conducted to determine which at-risk population groups would be prioritized for LTBI testing and treatment among 24 pre-defined population groups. Evidence on

increased prevalence of LTBI, risk of progression from LTBI to active TB disease and increased incidence of active TB was available for the following 15 risk groups: (i) adult and child TB contacts, (ii) health-care workers and students, (iii) people living with HIV, (iv) patients receiving dialysis, (v) immigrants from high TB burden countries, (vi) patients initiating anti-tumour necrosis factor (TNF) therapy, (vii) illicit drug users, (viii) prisoners, (ix) homeless people, (x) patients receiving organ and haematologic transplantation, (xi) patients with silicosis, (xii) patients with diabetes, (xiii) people with harmful alcohol use, (xiv) tobacco smokers, and (xv) underweight people.

The first systematic review assessed the prevalence of *M. tuberculosis* infection as determined either by TST or commercially available IGRAs. A total of 276 studies (with 299 entries) were included. Comparison between LTBI prevalence among risk groups and prevalence among the general population was made using LTBI prevalence estimates derived from modelling *(2)*; and pooled risk ratios were calculated for the risk groups. A considerable heterogeneity in risk ratios was observed. Nevertheless, increased risk of LTBI was reported for both TST and IGRA in at least 65% of the studies for the following risk groups: prisoners, homeless people, elderly people, immigrants from high TB burden countries, adult and child TB contacts, and illicit drug users.

A second systematic review assessed the risk of progression from LTBI to active TB. Eight individual studies provided the evidence of an increased risk of progression for the following categories: people living with HIV, adult contacts of TB cases, patients undergoing dialysis, underweight people, individuals with fibrotic radiologic lesions and recent converters to the TST.

The third systematic review was conducted to compare the pooled incidence rate ratio of active TB in the pre-defined risk groups compared with the general population. Data of increased risk of active TB were reported in the following risk groups: people living with HIV, adult and child contacts to a TB case, patients with silicosis, health-care workers (including students), immigrants from high TB burden countries, prisoners, homeless, patients receiving dialysis, patients receiving anti-TNF drugs, patients with cancer, people with diabetes mellitus, people with harmful alcohol use, tobacco smokers and underweight people.

2.1.2. Balance of benefits and harms

The Panel reviewed the evidence generated from the systematic reviews and discussed each of the population risk groups identified in detail for the prevalence of latent TB, risk of progression into active TB and the incidence of active TB compared with the general population. The Panel concluded that there is clear evidence of benefit from systematic testing and treating of LTBI in the following groups: people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis.

The Panel concluded that the evidence of benefits outweighing harms in the following population risk groups is weak, but judged that the benefits of systematic testing and treating may outweigh the harms: health-care workers, immigrants from high TB burden countries, prisoners, homeless persons and illicit drug users. The decision to systematically test for and treat LTBI in these population groups should be in accordance with local TB epidemiology and context, health system structures, availability of resources and overall health priorities. Priority must be given to individuals with history of recent infection status conversion, tested either by IGRA or TST, from negative to positive. Similarly, the Panel concluded that recent immigrants from high TB burden countries to low TB burden countries should be prioritized. However, the Panel underscored that a person's status —tested positive for LTBI or receiving LTBI treatment — should not affect the process, procedure and status of immigration.

The Panel noted the paucity of data on the benefits and harms of systematic latent TB testing and treatment in diabetic patients, people with harmful alcohol use, tobacco smokers and underweight people and concluded that the benefits of systematic and routine testing and treatment in these risk groups do not outweigh the risks unless individuals/patients also belong to the groups mentioned in the above recommendations.

The Panel recognized the potential limitations of the systematic reviews, which were restricted to a single database (Medline) over a 10-year period for both the comparison of prevalence of LTBI and progression to active TB disease in a specific risk group over the general population. It also noted that the inclusion of studies with no restriction on publication year or language through contacting 30 experts in the field mitigated this limitation. The Panel judged that the available evidence was adequate to issue the recommendations particularly taking into consideration the urgent need for WHO guidelines. It also emphasized the importance of further research on the benefits and harms of LTBI testing and treatment in persons with silica exposure, patients receiving steroid treatment, patients with rheumatologic conditions, indigenous populations and cancer patients.

2.1.3. Values and preferences of clients and health-care providers

Individual benefit outweighing risk should be the mainstay of latent TB testing and treatment. The Panel agreed that prioritization of groups based on their risk and the local and national context (e.g. epidemiology, resource availability) will be acceptable by individuals as well as key stakeholders including clinicians and programme managers. It was noted that the high risk of ongoing TB transmission in certain risk groups, such as health-care workers (including students), prisoners (including prison staff), homeless and illicit drug users, require attention so that the benefit of treatment is not compromised through reinfection. The TB prevention value of antiretroviral therapy for people living with HIV was also noted.

2.1.4. Resource considerations

The decision of national TB programmes and other stakeholders to identify the priority risk groups for programmatic management of LTBI needs to consider availability and efficient use of resources. The Panel noted that prioritizing high-risk groups, such as people living with HIV, immigrants from high TB burden countries and contacts with TB cases for latent TB testing and treatment have the potential to yield savings for the health-care system. However, cost-effectiveness analyses based on rigorous empirical data are scarce for other risk groups.

2.2. Algorithm to test and treat LTBI

- Individuals should be asked about symptoms of TB before being tested for LTBI. Chest radiography can be done if efforts are intended also for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions. *(Strong recommendation, very low quality of evidence)*
- Either TST or IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000. *(Strong recommendation, very low quality of evidence)*
- IGRA should not replace TST in low-income and other middle-income countries. *(Strong recommendation, very low quality of evidence) (8)*

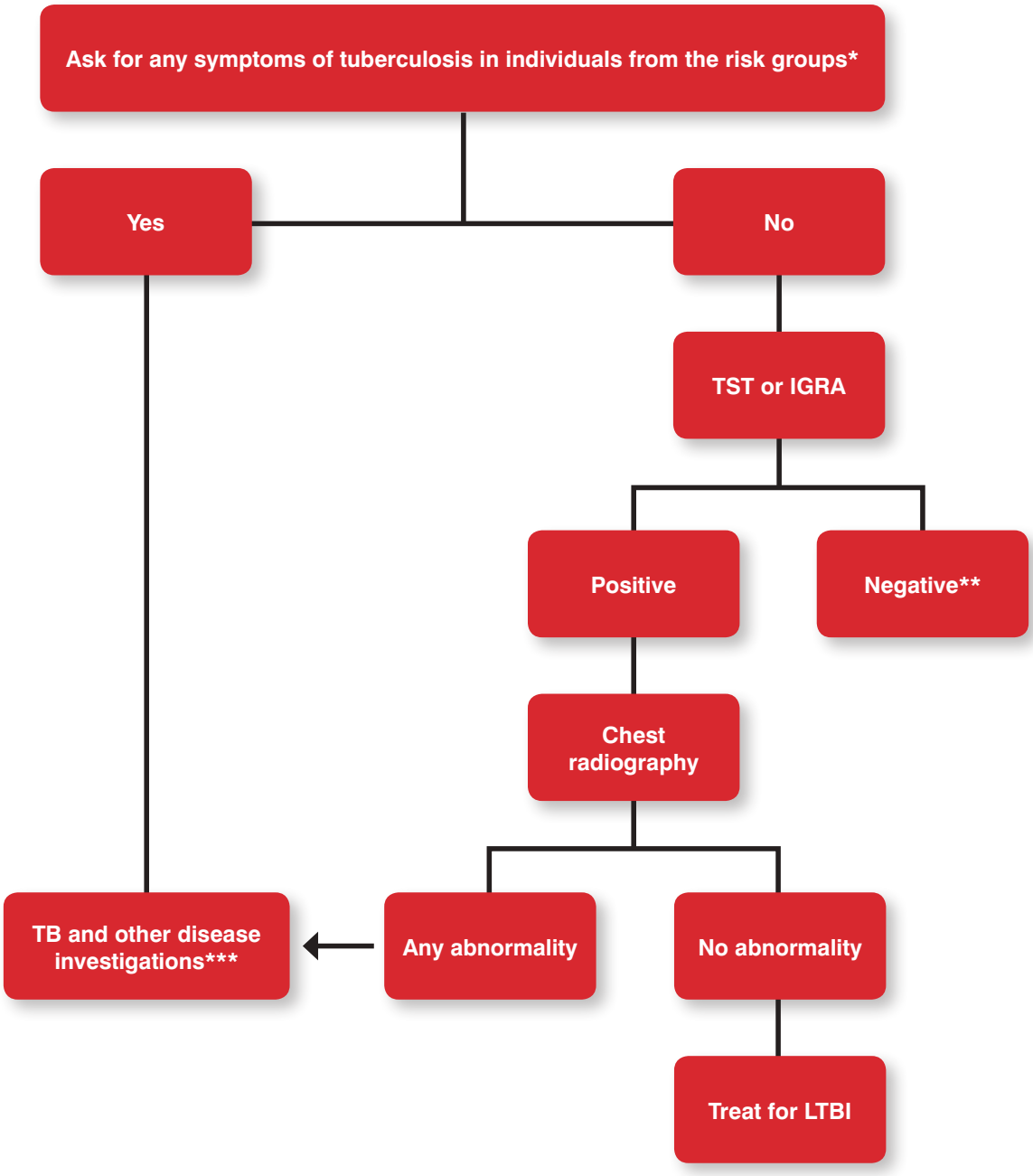
Remark: *HIV testing should be incorporated into the medical evaluation of LTBI treatment candidates based on national or local policies.*

The rationale for the Panel's decision for a strong recommendation for symptom screening and chest radiography prior to initiating treatment was due to the crucial importance of exclusion of active TB disease and inclusion of LTBI for better patient outcomes. Similarly, the rationale for a strong recommendation that IGRA should not replace TST in low-income and other middle-income countries, despite the very low level of evidence, is justified by the Panel's consideration of patient relevant outcomes, performance of the test in these settings and costs *(8)*.

2.2.1. Summary of the evidence

A systematic review was conducted to determine the sensitivity and specificity of symptoms, and chest radiography screening for active pulmonary TB in HIV-negative persons and persons with unknown HIV status. The review identified 11 studies from general population surveys that provided

Figure 1. Algorithm for targeted diagnosis and treatment of LTBI in individuals from risk groups



* Any symptoms of TB include any one of: cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue. HIV test could be offered based on national or local guidelines or clinical judgment. Similarly chest radiographs can be done if efforts are intended also for active TB case finding.

** Clients for whom LTBI treatment is not indicated should be provided information about TB including on the importance of seeking care if symptoms of TB developed.

*** National TB guidelines should be followed while investigating for TB. In addition, those individuals in whom TB is excluded after investigations (including individuals with fibrotic radiologic lesions) can be considered for LTBI treatment.

data on screening with either symptoms or with chest radiography or with both. To illustrate how different screening and diagnostic algorithms are expected to perform in ruling-out active TB, a model was constructed to compare the following seven screening strategies: (i) any TB symptom, (ii) chest radiography with any abnormality, (iii) a combination of chest radiography with any abnormality or any TB symptom, (iv) chest radiography with suggestive TB abnormalities, (v) cough more than 2–3 weeks, (vi) if there is cough more than 2–3 weeks then chest radiography as a follow up test, and (vii) if any TB symptom is present then chest radiography. The combination of any abnormality in chest radiography and/or presence of any TB suggestive symptoms (i.e. any one of cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) would offer the highest sensitivity and negative predictive value to rule out TB.

A systematic review was conducted to explore tests and clinical proxies that can best identify individuals most-at-risk of progression to incident TB disease. While the systematic review did not identify any clinical parameters that would assist in the prediction of progression to active TB diseases, 29 studies were about the predictive utility of IGRA and TST. The main effect measure of interest was the *risk ratio*, comparing TB incidence following a positive test results versus a negative test result in individuals not receiving preventive therapy, or alternatively the *incidence rate ratio* in the few studies that reported the person years of follow-up amongst test positives and test negatives. The overall pooled risk ratio estimate for the TST was 2.64 (95% CI: 2.04–3.43, n = 22 studies) and 8.45 (95% CI: 4.13–17.31, n = 16 studies) for IGRA. The pooled risk ratio estimate for IGRA was 13.55 (95% CI: 6.08–30.21) in high-income and upper middle-income countries with TB incidence less than 100 per 100 000 compared to 2.32 in the remaining countries (95% CI: 1.41–3.81).

Because it was difficult to judge if the differences in the pooled estimates of risk ratios for TST and IGRA were due to true differences between the tests or if they reflected the result of heterogeneous study populations included in the analysis, the main data analysis was limited to the eight studies that compared TST and IGRA to each other in the same study population (head-to-head analysis). This analysis showed the pooled risk ratio estimate for TST to be 2.58 (95% CI: 1.72–3.88) and for IGRA 4.94 (95% CI: 1.79–13.65). The pooled risk ratio in the three studies that evaluated both the TST and IGRA was 2.07 (95% CI: 1.38–3.11) for the TST and 2.40 (95% CI: 1.26–4.60) for IGRA. In both analyses, the confidence intervals around effect measures for the TST and IGRA overlapped and were imprecise. There was insufficient data to provide evidence on predictive utility of the tests among specific high-risk subpopulations or groups.

Table 1:
Pooled estimates in the predictive utility of IGRA and TST in head-to-head studies that evaluated incident active TB in untreated individuals

Outcome	Pooled estimate of TST	I^2 (P-value)	Pooled estimate of IGRA	I^2 (P-value)	Remark
Risk ratio (8 studies)	2.58 (95% CI: 1.72–3.88)	14% (0.320)	4.94 (95% CI:1.79–13.65)	72.3% (0.001)	*Systematic review to complement this information with additional clinical and other parameters did not yield results*
Incidence risk ratio (3 studies)	2.07 (95% CI: 1.38–3.11)	0% (0.604)	2.40 (95% CI: 1.26–4.60)	41% (0.183)	

2.2.2. Balance of benefits and harms

The Panel reviewed the evidence generated from the systematic reviews and discussed benefits and harms of the alternative screening options to rule out active TB. The Panel noted the potential limitation of using data from the general population as a proxy for ruling out active TB among at-risk populations. However, it concluded that this would have no implication in the development of the algorithm that will be used to test and treat individuals from high-risk populations. The Panel reiterated that active TB disease should be excluded before LTBI testing and treatment.

2.2.3. Values and preferences of clients and health-care providers

Symptom screening and chest radiography were considered acceptable for individuals and programme managers, and the benefit outweighs increased costs and logistic demand.

The Panel noted that comparative analysis between TST and IGRA in the head-to-head studies showed no evidence that one test should be preferred over the other to assess progression to TB disease. The Panel also noted that equity and access could vary depending on the type of test used. For example, the single visit required for IGRA compared to two consultation visits required for TST may favour client preferences. However, the Panel could not be confident of the overall programmatic impact of this in terms of access and equity for clients due to the additional cost required. It was noted that serial testing for LTBI including for health-care workers was beyond the scope of these guidelines.

2.2.4. Resource considerations

The Panel noted that resource requirements could vary and that the decision to implement LTBI testing and treatment needs to consider several factors, including the structure of the health system, feasibility of implementation, infrastructure requirements and Bacillus Calmette–Guérin (BCG) vaccination coverage. The Panel noted that the incremental cost-effectiveness of IGRAs compared to TST appeared to be influenced mainly by the accuracy of the two diagnostic tests, with BCG vaccination playing a decisive role in reducing the specificity of TST and leading the choice towards IGRA-only strategies. However, IGRAs are more costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing TST with IGRAs as a public health intervention in low-income and other middle-income countries is not recommended *(8)*.

2.3. Treatment options for LTBI

The following treatment options are recommended for the treatment of LTBI: 6-month isoniazid, or 9-month isoniazid, or 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone. *(Strong recommendation, moderate to high quality of evidence)*

Remark: *There was consensus of the Panel on the equivalence of 6-month isoniazid, 9-month isoniazid, and 3-month rifapentine plus isoniazid. However, the Panel could not reach a consensus and voted on the equivalence of 3–4 months isoniazid plus rifampicin and 3–4 months rifampicin alone as alternative options to 6-month isoniazid. Sixty per cent of the Panel members voted for 4-month rifampicin alone as an equivalent option to 6-month isoniazid while 53% voted for 3–4 months isoniazid plus rifampicin as an equivalent option to 6-month isoniazid. Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment due to potential drug-to-drug interactions. See annex 3 for drug dosage.*

2.3.1. Summary of the evidence

A systematic review was conducted to evaluate the efficacy and safety of treatment for LTBI *(11)*. Fifty three studies, all of which were randomized controlled trials and recorded at least one of the two pre-specified endpoints (preventing active TB, hepatotoxicity of Grade III or above), were included. Data from the systematic review was available for 15 treatment regimens, although relatively few direct comparisons were reported, some with sparse data, particularly for modern regimens. Pyrazinamide-containing regimens were excluded from further consideration because of reported toxicity. The estimate of the rates of severe hepatotoxicity and death of pyrazinamide-containing regimens was measured in comparison with an historical isoniazid control *(10)*. Rifampin-pyrazinamide combinations had fatality and hospitalization rates of 0.9 (95% CI: 0.4–1.9) and 2.8 (95% CI: 1.8–4.3) per 1000 rifampicin–pyrazinamide therapy initiations, respectively, compared with fatality rates of 0.0–0.3 deaths per 1000 persons in individuals under isoniazid preventive therapy.

No placebo or treatment trial directly compared the efficacy and safety of the 9-month isoniazid regimen. It was also noted that clinical trials comparing the 3-month regimen of weekly rifapentine plus isoniazid with placebo or no treatment were not available. This is because when the 3-month weekly rifapentine plus isoniazid regimen trials were being carried out,comparison with placebo/no treatment arms was not ethically acceptable.

The expert panel comparatively appraised the evidence on efficacy and safety of available treatment options. The results of the pair-wise comparisons with placebo are reported in Table 2 — isoniazid for 6 months was used as a reference comparator in the analysis of rates of incident TB, and hepatotoxicity (Grade III/IV) with other regimens (Table 3).

Table 2:
Regimens that showed significant efficacy when compared to placebo and profile of heptotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Placebo	Isoniazid 6 months	0.61 (0.48–0.77)	Low	0.99 (0.42–2.32)	Low
Placebo	Isoniazid 12–72 months	0.53 (0.41–0.69)	Low	0.59 (0.23–1.55)	Very low
Placebo	Rifampicin 3–4 months	0.48 (0.26–0.87)	Moderate	-	-
Placebo	Rifampicin and isoniazid 3–4 months	0.52 (0.33–0.84)	Low	-	-

In general these comparisons did not show the superiority of one regimen over any other. However, in terms of safety, a 3–4 months rifampicin regimen and a 3-month weekly rifapentine plus isoniazid regimen had fewer hepatotoxicity events compared to the 6-month and 9-month isoniazid regimen, respectively.

In the absence of any direct comparison of efficacy of 6- and 9-month isoniazid, the Panel reviewed a reanalysis of the United States Public Health Service (USPHS) trials conducted in the 1950s and 1960s that concluded that optimal protection from isoniazid appears to be obtained by nine months *(12)*. Based on this, the Panel judged that 9-month isoniazid can be considered as an equivalent treatment option to 6-month isoniazid.

Table 3:
Comparison of efficacy of 6-month isoniazid with other regimens for the development of incident TB and hepatotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Isoniazid 6-month	Rifampicin 3–4 months	0.78 (0.41–1.46)	Moderate	0.03 (0.00–0.48)	Low
Isoniazid 6-month	Rifampicin and isoniazid 3–4 months	0.89 (0.65–1.23)	Low	0.89 (0.52–1.55)	Very low
Isoniazid 6-month	3-month weekly rifapentine plus isoniazid*	1.09 (0.60–1.99)	Low	1.00 (0.50–1.99)	Low
Isoniazid 9-month	3-month weekly rifapentine plus isoniazid	0.44 (0.18–1.07)	Low	0.16 (0.10–0.27)	Moderate

*exclusively among people living with HIV.

2.3.2. Balance of benefits and harms

The Panel reviewed the evidence for efficacy of the different treatment regimens against incident TB compared to the placebo, the hepatotoxicity profile of each regimen, and the comparison of the different regimens against 6-month isoniazid as a reference. The Panel unanimously agreed on the equivalence of 6-month isoniazid, 9-month isoniazid and 3-month weekly rifapentine plus isoniazid regimens as alternative treatment options to each other. However, the Panel could not reach a consensus and voted on the equivalence of 3–4 months isoniazid plus rifampicin and 3–4 months rifampicin alone to 6-month isoniazid. Sixty per cent of the Panel members who attended the meeting voted for 3–4 months rifampicin alone as an equivalent option to 6-month isoniazid while 53% of them voted for 3–4 months isoniazid plus rifampicin as an equivalent option to 6-month isoniazid. For this reason, the Panel concluded that the following regimens can be recommended as options to treat LTBI: 6-month isoniazid, or 9-month isoniazid, or 3-month weekly rifapentine plus isoniazid, or 3–4 months rifampicin alone, or 3–4 months isoniazid plus rifampicin. The Panel also noted that the risk of hepatotoxicity is considerably low in children compared to adults *(13)*.

2.3.3. Values and preferences of clients and health-care providers

The Panel agreed that shorter duration regimens are preferred over longer duration regimens from the perspective of individuals receiving treatment, clinicians providing the treatment and programme managers, and concluded that the 3-month regimen of weekly rifapentine plus isoniazid has advantage over the other regimens. Similarly, the Panel agreed that 6-month isoniazid is preferred over 9-month isoniazid due to resource requirements, feasibility and acceptability by patients. The Panel noted the reported positive acceptability of rifampicin- and rifapentine-containing regimens by individuals receiving treatment, and further concluded that the rifampicin (3–4 months isoniazid plus rifampicin and 4-month rifampicin only) and isoniazid (6- and 9-month) containing regimens could be self-administered by individuals receiving treatment. The Panel noted that the 3-month weekly rifapentine plus isoniazid regimen should be given under direct observation as the evidence available so far is based on this circumstance. It also noted that such provision of rifapentine under direct supervision will lower acceptability by individuals receiving treatment. Therefore, it was strongly suggested to revisit this once further evidence is available on the value of self-administration. Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment due to potential drug-to-drug interactions. The Panel expressed concern about the current high cost of rifapentine and absence of registration in many countries that limits its availability, with consequent inequities in access.

2.3.4. Resource considerations

The Panel noted that different treatment options have different resource requirements and concluded that programme managers need to decide upon the treatment options taking into consideration their resource capacity and national and local context. The Panel further noted that the need for direct supervision of the 3-month weekly rifapentine plus isoniazid regimen increases resource requirements, in addition to the current high cost of the drug.

2.4. Preventive treatment for contacts of MDR-TB cases

Serious limitations of the quality of evidence prevent drawing any recommendations on MDR-TB preventive therapy as a public health measure. Strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases.

2.4.1. Summary of the evidence

A systematic review was conducted to define the effectiveness of anti-TB drugs in preventing active TB in contacts of MDR-TB patients. Four studies were included for the analysis; all were cohort studies of which one *(14)* was a prospective study exclusively involving children below 5 years of age while the others were retrospective studies involving both adults and children *(15–17)*. Drug regimens used for preventive treatment varied widely across the studies. For the final analysis, two of

the studies in which all or majority of MDR-TB contacts received preventive treatment with isoniazid *(14, 16)* were excluded. The other study contained only 11 contacts receiving a regimen with at least one active agent and was excluded because of its small size *(16)*. Therefore, the quality of evidence was determined only for one comparison study which used a tailored regimen taking into account the resistance pattern of the index case among childhood contacts *(14)*. In this single study two of 41 children receiving tailored preventive therapy developed TB (confirmed and probable TB) compared to 13 of 64 children not receiving preventive treatment (OR=0.2, 95% CI: 0.04–0.94).

2.4.2. Balance of benefits and harms

The Panel noted the scarcity of available evidence on effectiveness and safety of using anti-TB drugs to prevent active TB among adult and childhood contacts of MDR-TB cases. Regimens that can be used for the treatment of contacts with MDR-TB are known to have poor safety and tolerability particularly among adults. Additionally, regimens used for the treatment of contacts of MDR-TB cases, which are often composed of one or two drugs, are inadequate to treat active disease should this develop, carrying the further risk of acquisition of additional resistance. Many healthy children who will not develop MDR-TB will be placed on potentially toxic regimens for which paediatric formulations are unavailable. Moreover, the tailoring of regimens is further hampered by the lack of reliable drug susceptibility testing for certain drugs (e.g. ethionamide, pyrazinamide, ethambutol).

2.4.3. Values and preferences of clients and health-care providers

The Panel emphasized the urgent need for adequately powered randomized controlled trials to define the benefits and harms of treatment of MDR-TB contacts for clients and health-care providers. The Panel expressed its concern that wider use of treatment of MDR contacts without established evidence would set a precedent and challenge the conduct of essential clinical trials. In addition, it is noted that the infecting strains in the contact may have a different resistance pattern to those of the source case. This may happen because of coincidental infection from another index case, mixed strains in the index case, or infection from the index case before the strain in the latter acquired resistance. The lack of paediatric formulations for some drugs was mentioned as a concern.

2.4.4. Resource considerations

The Panel recognized that determination of the drug susceptibility profile for drugs to be used as preventive treatment for MDR contacts poses both technical and logistic challenges. Furthermore, the need for close clinical monitoring and follow-up of contacts and prescribing treatment regimens will incur extra costs and strain the capacity of MDR-treatment services. Broad implementation of preventive treatment may divert precious second-line drugs of proven effectiveness (levofloxacin, moxifloxacin and ethionamide) from curative services. The need for active pharmacovigilance for individuals put on preventive treatment for MDR-TB has resource implications *(18)*.

2.4.5. Conclusions

The Panel noted the serious limitations of the quality of evidence to draw any recommendations on MDR-TB preventive therapy as a public health measure. Weighing the lack of evidence against the severe consequences of developing MDR-TB, the Panel concluded that the management of contacts of MDR-TB patients needs to be guided by a comprehensive individual risk assessment that takes into consideration the balance between risk and benefits for the individual. Strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases. On the other hand, it should be noted that, in circumstances where there is a reasonable likelihood that the exposed person may have also been exposed to drug-susceptible TB, the individual should be given a course of standard LTBI treatment according to national guidelines. However, the Panel noted that clinicians as part of sound clinical practice can consider individually tailored treatment regimens based on the drug susceptibility profile of the index case particularly for child contacts below 5 years of age when benefits can outweigh harms with reasonable confidence, and keep in mind the technical shortcomings of drug susceptibility testing for many of the second-line anti-TB drugs. In individual cases where preventive therapy is considered for contacts of MDR-TB cases, the programme needs to ensure that the necessary resources are in place to provide quality-assured drug susceptibility testing, all the necessary medications, and to monitor closely for harms, breakthrough disease and acquired resistance.

3. Issues in Implementation

3.1. Adverse events monitoring

Individuals who receive treatment for LTBI do not have active disease, and therefore, it is mandatory to minimize risks during treatment. Drug-specific adverse reactions can occur with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity); rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity). While most adverse drug reactions are minor and occur rarely, the Panel noted that maximum attention should be paid to prevention of drug-induced hepatotoxicity.

A systematic review was conducted to assess the best way to monitor and manage hepatotoxicity and other adverse drug reactions, but no studies were identified. A review of national guidelines *(19–23)* showed the presence of consistent recommendations across the different guidelines based on expert opinion, which were useful to inform the judgment of the Panel.

The Panel underlined the importance of routine regular clinical monitoring of individuals receiving treatment for latent TB through a monthly visit to health-care providers. The prescribing health-care provider should explain the disease process and the rationale of the treatment and emphasize the importance of completing the treatment. Those receiving treatment should be educated to contact their health-care providers should they develop symptoms, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. Whenever a health-care provider cannot be consulted at the onset of these symptoms, treatment should be immediately stopped.

The Panel noted that there was insufficient evidence to support baseline laboratory testing for measurements of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin. However, the Panel strongly encourages baseline laboratory testing for individuals with the following risk cofactors: history of liver disease; regular use of alcohol; chronic liver disease; HIV infection; age more than 35 years; and pregnancy or the immediate postpartum period (i.e., within three months of delivery). For individuals with abnormal baseline test results, routine periodic laboratory testing should be done.

3.2. Risk of drug resistance following LTBI treatment

A systematic review was conducted to determine whether LTBI treatment leads to significant development of resistance. The systematic review considered the following treatment regimens:

Isoniazid for 6- to 12-month duration: Thirteen studies comparing 6- to 12-month isoniazid preventive therapy versus no treatment or placebo were included in the systematic review (seven involving HIV uninfected populations); no difference in the risk of resistance among incident TB cases was found (risk ratio = 1.45 (95% CI: 0.85–2.47)). There was little evidence of heterogeneity ($p=0.923$) and the risk ratio for HIV-uninfected and HIV-infected populations was comparable. The quality of the evidence was moderate.

Isoniazid for 36 months in HIV-infected individuals: Three studies comparing 36- and 6-month isoniazid were reviewed but only one study provided resistance rates, and no significant difference in drug resistance was found (risk ratio = 5.96 (95% CI: 0.24–146) *(24)*. The two other studies reported that the observed proportion of resistant cases were similar to the expected rate in the background population, but did not provide a direct comparison of resistance rates between those receiving 36 months compared to those receiving 6 months treatment *(25,26)*. Therefore, it was concluded that there is no evidence to indicate whether or not continuous use of isoniazid increases the risk of isoniazid resistance.

Rifamycin-containing regimens: Five studies were included in the comparison of rifamycin resistance in individuals treated with a rifamycin-containing regimen versus regimen not containing rifamycin. There were very few cases of rifamycin resistance, a total of six (0.1%) cases in 5790 individuals receiving LTBI treatment with a rifamycin and five (0.09%) cases in the 5537 individuals in the control group with a relative risk of 1.12 (95% CI: 0.41–3.08). The quality of the evidence was very low after downgrading for risk of bias, indirectness and imprecision.

The Panel concluded that the available evidence showed no significant association between anti-TB drug resistance and the use of isoniazid and rifamycins for LTBI. However, the Panel noted the very low quality of evidence, particularly for rifamycin regimens. In light of this, the Panel emphasized the importance of excluding active TB disease using all available investigations according to national TB guidelines and taking into account the recommendations provided in Section 2.2. The importance of establishing national TB drug resistance surveillance systems in countries implementing national latent TB management programmes was emphasized.

3.3. Adherence and completion of preventive treatment

Adherence to the full course and completion of treatment are important determinants of clinical benefit to the individual as well as to the success of the programme.

A systematic review was conducted to explore the interventions that are effective to improve initiation, adherence and completion of treatment for LTBI. Twenty articles reported on LTBI treatment initiation rate and 35 on treatment completion rate in eight different population groups reviewed. Completion rates were shown to vary greatly across risk groups, with pool estimates ranging from 22% (95% CI: 6%–43%) in prisoners to 82% (95% CI: 66%–94%) in people living with HIV. In general, completion rates were lower among prisoners and immigrants compared with people living with HIV and contacts, and were inversely proportional to the duration of treatment.

Thirty-three articles were included for the determinants of treatment initiation, adherence and completion. The analysis identified the following 10 determinants as detrimental to treatment completion: (i) adverse drug reactions, (ii) longer duration of treatment, (iii) immigrant status, (iv) long distance from health facility, (v) history of incarceration, (vi) absence of perception of risk, (vii) presence of stigma, (viii) alcohol and drug use, (ix) unemployment, and (x) time lag between diagnosis and treatment.

Evidence on the efficacy of interventions to improve treatment adherence and completion was obtained from 17 articles. Shorter treatment duration was significantly associated with increased adherence in two randomized trials (OR = 1.5, 95% CI: 1.0–2.3) *(27,28)*. One randomized trial showed a significant increase in completion rate in the 3-month weekly rifapentine plus isoniazid regimen compared to the 9-month isoniazid regimen *(29)*. However, this study was confounded by the fact that the shorter regimen was also administered under direct observation. There is contradictory evidence on the role of monetary incentives to improve treatment completion rates: while two randomized trials showed benefit of incentives (either monetary or methadone) on treatment completion rates among illicit drug users (OR = 18.4, 95% CI: 7.7–43.7) *(30,31)*, two other randomized trials among the homeless *(32)* and inmates *(33)* did not show any significant impact of monetary incentives in improving treatment completion rates. Significant increases in completion rates were demonstrated with peer-support and coaching among adolescents and adults (OR = 1.4, 95% CI: 1.1–1.9) *(34–36)*; nurse case management among homeless (OR = 3.01, 95% CI: 2.15–4.20) *(37)*; cultural case management among immigrants (OR = 7.8, 95% CI: 5.7–10.7) *(38)*; and educational interventions among inmates (OR = 2.2, 95% CI: 1.04–4.72) *(33)*.

The Panel noted that the available evidence is heterogeneous and inconclusive to recommend on the best interventions to improve adherence and completion of treatment. However, the Panel underlined the importance of introducing interventions that are responsive to the specific needs of the risk groups. National TB programmes should design flexible interventions that are tailored to respond to the local context and needs of the population to ensure acceptable initiation of, adherence to and completion of LTBI treatment.

3.4. Ethical considerations

In addition to the general ethical considerations in TB programmes *(39)*, LTBI testing and treatment raises a range of ethical issues. First, latent TB is by definition an asymptomatic state and this alters ethical obligations that would be imposed by active TB. For example, the lack of immediate risk of transmission associated with LTBI makes it unethical to restrict migration policy based on the status of LTBI in the individual *(40)*. Secondly, the uncertainty regarding accurate assessment of individual risk for development of active TB poses a challenge in communication. Such concepts need to be sensitive to the local cultural and social context to be adequately understood during the informed consent process for both screening and treatment. Thirdly, latent TB disproportionately affects individuals and groups that are already socially and medically vulnerable and as such special efforts are needed to ensure that significant vulnerability in target groups does not affect the validity of consent or limit the effectiveness of public health interventions.

There is strong moral justification for appropriate national policies and practices to reduce the impact of latent TB, particularly in vulnerable groups. Policies should also be evaluated under an ethical perspective after implementation, both to consider possible unexpected impact and to ensure that the evidence on which they are based remains current and relevant *(41)*.

3.5. Cost effectiveness

A systematic literature review was conducted to critically appraise and summarize current evidence on the cost-benefit and cost-effectiveness associated with screening for and treatment of LTBI. Studies that evaluated costs and outcomes of any screening strategy and any drug regimen for LTBI compared to no intervention in any setting and population group were selected. The outcomes considered were incremental cost per quality-adjusted life year or life year gained, and incremental cost per TB case averted. Thirty nine articles were included and the majority of articles (82%) reported on analyses conducted in upper middle-income countries with TB incidence less than 100 in 100 000 population.

Cost inputs (adjusted for currency and inflation to US$ value as of 2012), varied widely among studies; such as the cost of testing for detecting LTBI using TST varied from US$ 10.9 in a study from Italy to an average of US$ 31.5 in studies from the UK. Similarly, detecting LTBI using IGRA test varied from US$ 22.5 in a study from Mexico to an average of US$ 97.1 in studies from the UK. Wide variations were also observed for the cost of screening of eligible candidates for latent TB treatment and the overall cost. For example, the costs of side-effects monitoring (including liver function tests and clinical monitoring) ranged from US$ 8.3 to US$ 687.3. The average cost of treating LTBI (including cost of drugs and monitoring) ranged from US$ 381.9 in Italy to US$ 1 129.9 in the UK.

Studies showed that testing and treating immigrants from high TB incidence countries (above 120–150 per 100 000) to low TB incidence countries may determine savings for the health-care system or have a favourable incremental cost-effectiveness ratio. Similar results were found in studies among people living with HIV and contacts of patients with active TB.

In conclusion, the available evidence suggests that screening for and treatment of LTBI may be a cost-effective intervention for population groups characterized by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high TB incidence countries, contacts of active TB cases and persons living with HIV. However, a marked variability across studies in economic inputs, in epidemiologic and TB natural history parameters, as well as in assumptions on effectiveness of preventive treatment made the extrapolation measures of cost-effectiveness from one setting to another problematic.

3.6. Programme management, monitoring and evaluation

The introduction of treatment for LTBI as a public health intervention entails the documentation of treated individuals through functional and routine monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems. Appropriate recording and reporting tools

need to be developed, and standardized indicators established to regularly inform decision making for programme implementation. In some instances, these may require changes in the national legal and policy framework that has to be addressed according to the local and national context.

Critical public health considerations for routine monitoring and evaluation include: initiation and completion of treatment, active surveillance of adverse events and the development of active TB during and after the completion of treatment for latent TB. Additionally, programme monitoring is needed to evaluate quality, programme effectiveness and impact. Nationally standardized indicators and data capturing mechanisms are also required.

The Panel further noted that national TB programmes need to create a conducive policy and programmatic environment, including the development of national and local policies and standard operative procedures to facilitate the implementation of the recommendations in these guidelines. This could include promoting universal health coverage, prioritizing the risk groups based on the epidemiology of TB, health infrastructure and programmatic management issues. Furthermore, dedicated resources need to be allocated including for human resource development and service delivery.

4. Research gaps

The review of the evidence for formulating the recommendations exposed a number of upstream research gaps to better understand, diagnose and treat LTBI. These could include the development of diagnostic tests with improved performance and predictive value for reactivation TB and drugs that can cure LTBI or that can be provided for short duration and with less adverse events as an urgent measure. There is also a need for intensified research to identify suitable biomarkers and drugs selectively acting on non-dividing *M. tuberculosis*. In addition to these fundamental research gaps, the following priority research gaps were identified to inform the revision of these guidelines. It is imperative that donors and the scientific research community respond to these gaps in order to update the guidelines and optimize programme implementation.

4.1. Risk of progression to active TB disease and differential impact by population risk group

Measuring the risk of progression from LTBI to active disease in a number of risk groups is crucial to determine the potential benefits of LTBI treatment and design appropriate public health interventions. In addition to direct measurement of incidence in cohort studies (such as TST positive cohort in a risk group versus TST positive cohort in the general population), alternative methods can be explored (such as the use of genotyping to measure the risk of reactivation in comparison studies). Generating evidence on the benefits and harms of systematic treatment of LTBI in all risk groups and particularly the following groups is essential: diabetic patients, people with harmful alcohol use, tobacco smokers, underweight people, persons with silica exposure, patients receiving steroid treatment, patients with rheumatologic conditions, indigenous populations and cancer patients.

In addition, evidence needs to be generated on differential harm of LTBI testing and treatment in specific risk groups, on differential acceptability of testing and treatment, and on potential socially adverse events (such as stigma).

4.2. Defining the best algorithm to test and treat LTBI

Operational and clinical studies to identify undiagnosed active TB before LTBI treatment initiation are important. These could include assessing the diagnostic performance of the algorithm proposed in these guidelines with carefully designed appropriate studies as a priority. In addition, diagnostic algorithms tailored to the needs of specific risk groups should be developed and evaluated for performance, ease and capacity to assist in its implementation.

4.3. Treatment options for LTBI and adverse event monitoring

The development of treatment regimens that are shorter and better tolerated compared with those recommended in these guidelines is a priority for research. Studies to measure efficacy and the risk of toxicity and adverse events in specific risk groups (e.g. people who use drugs or people with alcohol use disorder) are essential. Drug interactions between rifamycin-containing regimens and antiretroviral drugs (including second- and third-line drugs) among people living with HIV are another priority gap that needs to be addressed.

Prospective, randomized studies are required to measure the incremental benefits of routine monitoring of liver enzymes over education and clinical observation alone in terms of preventing severe clinical adverse events. It is of paramount importance to stratify this evidence by population risk groups. This knowledge would be greatly beneficial in terms of cost-effectiveness, as routine laboratory monitoring could be costly and unfeasible.

4.4. Risk of drug resistance following LTBI treatment

Programme-based surveillance systems and clinical studies are needed to monitor the risk of drug resistance following LTBI treatment. Special consideration needs to be given to rifamycin-containing regimens because of the dearth of data. Similarly, studies on the efficacy of currently recommended treatment options in areas of highly prevalent drug resistance are required.

4.5. Adherence and completion of treatment

Carefully designed studies, including randomized clinical trials, are required to generate evidence on the effectiveness of context-specific interventions to enhance adherence and treatment completion. Such studies should be tailored to specific risk groups, with consideration to available resources and infrastructure of the health system.

4.6. Cost-effectiveness studies

Many cost-effectiveness evaluations are available in the literature, but their extensive heterogeneity prevents the comprehensive appraisal of cost-effectiveness of LTBI management interventions, stratified by population groups and type of intervention. Direct measurement of cost-effectiveness in specific settings and populations would be vital to expand the LTBI strategy at the national or local level.

4.7. Preventive treatment for MDR-TB contacts

Adequately powered randomized controlled trials are necessary to define the benefits and harms of treatment of MDR-TB contacts. Trials should be performed in both adult and paediatric populations with specific focus on the risk–benefit ratio. The composition, dosages and duration of the LTBI regimen for MDR-TB need to be optimized and the potential role of newer drugs with good sterilization properties should be investigated. Studies should examine the adverse effects of the long-term use of fluoroquinolones in preventive treatment. Improved strategies to reinforce pharmacovigilance should be developed.

4.8. Programme management

Epidemiological research is needed to understand the burden of LTBI and inform the development of nationally and locally tailored interventions. Similarly, standard approaches and tools need to be developed and assessed to monitor and evaluate the public health impact of programmatic implementation of LTBI management.

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Annex 1: Primary target countries for the guidelines on LTBI management*

Country name	Income status	Estimated TB incidence per 100 000 (2013)
Albania	upper-middle	18
Algeria	upper-middle	81
American Samoa	upper-middle	18
Andorra	high	7.3
Antigua and Barbuda	high	13
Argentina	upper-middle	24
Aruba	high	12
Australia	high	6.2
Austria	high	8.4
Azerbaijan	upper-middle	85
Bahamas	high	9.8
Bahrain	high	18
Barbados	high	1.4
Belarus	upper-middle	70
Belgium	high	9.1
Belize	upper-middle	37
Bermuda	high	0
Bosnia and Herzegovina	upper-middle	46
Brazil	upper-middle	46
Brunei Darussalam	high	58
Bulgaria	upper-middle	29
Canada	high	5
Cayman Islands	high	9.8
Chile	high	16
China	upper-middle	70
China, Hong Kong SAR	high	76
China, Macao SAR	high	88
Colombia	upper-middle	32
Costa Rica	upper-middle	11

Country name	Income status	Estimated TB incidence per 100 000 (2013)
Croatia	high	13
Cuba	upper-middle	9.3
Curaçao	high	1.4
Cyprus	high	5.8
Czech Republic	high	5.5
Denmark	high	7
Dominica	upper-middle	4.8
Dominican Republic	upper-middle	60
Ecuador	upper-middle	56
Estonia	high	22
Fiji	upper-middle	36
Finland	high	5.7
France	high	8.8
French Polynesia	high	22
Germany	high	5.8
Greece	high	5
Grenada	upper-middle	4.1
Guam	high	33
Hungary	upper-middle	18
Iceland	high	3.6
Iran (Islamic Republic of)	upper-middle	21
Iraq	upper-middle	45
Ireland	high	8.8
Israel	high	5.8
Italy	high	5.7
Jamaica	upper-middle	6.6
Japan	high	18
Jordan	upper-middle	5.8
Korea, Republic of	high	97
Kuwait	high	24
Latvia	high	50

* For practical purposes (such as analysis of systematic reviews) these countries were labelled as Category A countries whereas the rest of the countries were labelled Category B.

Country name	Income status	Estimated TB incidence per 100 000 (2013)
Lebanon	upper-middle	16
Libya	upper-middle	40
Lithuania	high	65
Luxembourg	high	8.7
Malaysia	upper-middle	99
Maldives	upper-middle	40
Malta	high	11
Mauritius	upper-middle	21
Mexico	upper-middle	21
Monaco	high	2.1
Montenegro	upper-middle	21
Netherlands	high	6.1
New Caledonia	high	19
New Zealand	high	7.3
Northern Mariana Islands	high	70
Norway	high	8.2
Oman	high	11
Palau	upper-middle	44
Panama	upper-middle	48
Poland	high	22
Portugal	high	26
Puerto Rico	high	1.6
Qatar	high	40
Romania	upper-middle	87
Russian Federation	high	89
Saint Lucia	upper-middle	5.7
Saint Vincent and the Grenadines	upper-middle	24
San Marino	high	1.5
Saudi Arabia	high	14
Serbia	upper-middle	18
Seychelles	upper-middle	30
Singapore	high	47
Sint Maarten	high	5.1
Slovakia	high	7.7
Slovenia	high	7.5

Country name	Income status	Estimated TB incidence per 100 000 (2013)
Spain	high	13
St. Kitts and Nevis	high	0
Suriname	upper-middle	39
Sweden	high	7.2
Switzerland	high	6.6
The former Yugoslav Republic of Macedonia	upper-middle	17
Tonga	upper-middle	13
Trinidad and Tobago	high	21
Tunisia	upper-middle	32
Turkey	upper-middle	20
Turkmenistan	upper-middle	72
Turks and Caicos Islands	high	6.9
United Arab Emirates	high	1.8
United Kingdom	high	14
United States	high	3.3
Uruguay	high	30
US Virgin Islands	high	7.7
Venezuela (Bolivarian Republic of)	upper-middle	33

Annex 2:
List of systematic reviews conducted

Systematic review 1: What is the prevalence of LTBI among risk groups?

Systematic review 2: What is the risk of progression of LTBI to active TB disease among risk groups.?

Systematic review 3: What is the incidence of active TB among risk groups?

Systematic review 4: Among individuals at risk of LTBI, which investigations and clinical parameters are most predictive of the absence of active TB?

Systematic review 5: Among persons at high risk of latent tuberculosis infection (LTBI) who are not on tuberculosis preventive therapy, which test(s) alone or in combination with other proxies for LTBI, when positive, can best identify individuals most at risk of progression to incident tuberculosis (TB) disease?

Systematic review 6: Systematic literature review and meta-analysis on the best treatment options for latent tuberculosis infection

Systematic review 7: What is the best way to monitor and manage hepatic toxicity and other adverse events in individuals receiving treatment for LTBI?

Systematic review 8: Does treatment for LTBI lead to significant development of resistance against the drugs used?

Systematic review 9: What is the effectiveness of anti-tuberculosis drugs (any regimen) in preventing active TB in contacts of MDR-TB patients?

Systematic review 10: For each recommended LTBI treatment regimen, what are the initiation and completion rates?

Systematic review 11: For each recommended LTBI treatment regimen, what are the determinants of treatment initiation, adherence and completion?

Systematic review 12: In individuals who are eligible for LTBI treatment, what are the interventions with demonstrated efficacy to improve LTBI treatment initiation, adherence and completion?

Systematic review 13: Will duration of protection from LTBI treatment be a barrier to LTBI management implementation?

Systematic review 14: What is the cost-effectiveness of LTBI management interventions?

Annex 3: Recommended drug dosage

Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5 mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults= 10 mg/kg Children = 10 mg/kg	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin= 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Adults and Children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg	Isoniazid = 900 mg Rifapentine = 900 mg

World Health Organization

For further information, please contact:

World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Global TB Programme
E-mail: tbdocs@who.int
Web site: www.who.int/tb

9789241548908