WHO consolidated guidelines on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment

Second edition

World Health Organization

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WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition

ISBN 978-92-4-009619-6 (electronic version)
ISBN 978-92-4-009620-2 (print version)

Suggested citation. WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

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Contents

Acknowledgements iv

Abbreviations and acronyms viii

Definitions ix

Executive summary xi

Introduction 1

1. Recommendations 3

1.1 Identifying populations for TB preventive treatment 3

1.2 TB screening and ruling out TB disease 9

1.3 Testing for TBI 19

1.4 TB preventive treatment options 21

2. Monitoring and evaluation 31

3. Research gaps 33

References 37

Annex 1. Recommendations in the WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment, second edition (2024) and in the previous edition (2020) 47

Annex 2. Methods and expert panels 52

Annex 3. GRADE summary of evidence tables 62

Annex 4. GRADE evidence-to-decision tables 102

Annex 5. Summary of unpublished studies (PICO 10) 221

A5.1 Summary of TB CHAMP and V-QUIN clinical trials 221

A5.2 Use of fluoroquinolones for TB preventive treatment in contacts of persons with MDR-/RR-TB: A systematic review 234

A5.3 Assessing fluoroquinolone (levofloxacin) acceptability among contacts of MDR-TB patients: a qualitative study 243

A5.4 A survey to explore the programmatic feasibility of levofloxacin (Lfx) TPT for MDR-TB contacts 246

Acknowledgements

The recommendations and the text of the *WHO consolidated guidelines on tuberculosis. Module 1: Prevention – tuberculosis preventive treatment, second edition* are the result of collaboration among professionals in various specialties with extensive expertise and experience in public health policy, tuberculosis (TB) programme management and the clinical care of TB patients. The recommendations in these guidelines were developed by successive guideline development groups (GDGs) convened by WHO, the latest of which met in December 2023. WHO gratefully acknowledges the contributions of all experts involved in preparation of these guidelines.[1]

The production and writing of these guidelines were coordinated by Avinash Kanchar, Dennis Falzon, Saskia den Boon and Matteo Zignol under the overall direction of Tereza Kasaeva, Director of the WHO Global Tuberculosis Programme.

Guideline Development Group

The GDG was composed of Mênonli Adjobimey (National TB Programme, Benin), Rolando Cedillos (University of El Salvador and Hospital Nacional Rosales, El Salvador), Ana Ciobanu (formerly National TB Programme, Republic of Moldova), Alexander Kay (Baylor College of Medicine, Eswatini), Naira Khachatryan (National TB Programme, Armenia), Amir Khan (Professional Association for Social Development, Pakistan), Blessina Kumar (Global Coalition of TB Advocates, India), Natalia Litvinenko (National Institute of TB and Lung Diseases, Ukraine), Nasehi Mahshid (TB Programme Manager, Tehran, Islamic Republic of Iran), Charisse Malbacias (Department of Health, Philippines), Alberto Matteelli (University of Brescia, Italy), Norbert Ndjeka (National Department of Health, South Africa), Senia Rosales Klintz (European Centre for Disease Prevention and Control, Sweden), Nicole Salazar Austin (Johns Hopkins Center for Clinical Global Health Education, United States of America [USA]), Susan Swindells (University of Nebraska, USA), Stavia Turyahabwe (Ministry of Health, Uganda) and Paran Winarni (Global Tuberculosis Community Advisory Board, Indonesia). The Chair of the GDG was Norbert Ndjeka, and the GRADE methodologist was Lawrence Mbuagbaw (McMaster University, Canada).

External reviewers

The External Review Group (ERG) was composed of Helen Ayles (London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland [United Kingdom]), Anurag Bhargava Yenepoya Medical College Hospital, India), Gavin Churchyard (The Aurum Institute, South Africa), Raquel Duarte (European Respiratory Society and University of Porto, Portugal), Amita Gupta (Johns Hopkins University, USA), Anthony D Harries (International Union Against Tuberculosis and Lung Disease, France), Nino Lomtadze (National TB Programme, Georgia), Ruslan Malyuta (UNICEF), Giovanni B. Migliori (Maugeri Research Centre, Italy), Lindiwe Mvusi (National Department of Health, South Africa), Anastasia Samoilova (National TB Programme, Russian Federation), Alena Skrahina (Republican TB Centre, Belarus), Carrie Tudor (Johns Hopkins University School of Nursing, USA) and Valentina Vilc (National TB Programme, Republic of Moldova).

[1] More information on the areas of expertise, gender and geographical distribution, declarations of interests and the management of potential conflict of members of the 2023 GDG and the External Review Group are summarized in Annex 2.

Evidence reviewers

Harsimren Sidhu, Stephanie Law and Richard Menzies (McGill University, Canada) undertook the systematic evidence review, the country survey on feasibility and the qualitative study of contacts, and provided summaries of the research for the GRADE evidence-to-decision table on use of levofloxacin in contacts exposed to multidrug-resistant TB (PICO 10; see annexes 3-5). The following presented the findings of studies relevant to the PICO question to the GDG: Gregory Fox (University of Sydney and Woolcock Institute of Medical Research, Australia), Anneke Hesseling and Thomas Wilkinson (Stellenbosch University, South Africa), Trinh Duong (University College London, United Kingdom), Leonardo Martinez (Boston University, USA) and James Seddon (Imperial College London, United Kingdom).

WHO Guideline Steering Group

The Guideline Steering Group was composed of Annabel Baddeley, Annemieke Brands, Saskia den Boon, Dennis Falzon, Nazir Ismail, Avinash Kanchar, Cecily Miller, Fuad Mirzayev, Sabine Verkuijl, and Matteo Zignol (WHO Global Tuberculosis Programme); Françoise Renaud, Marco Antonio De Avila Vitoria and Elena Vovc (Global HIV, Hepatitis and STIs programmes); Andreas Reis (Office of the Chief Scientist); Lorenzo Moja (Division of Access to Medicines and Health Products); Jean-Louis Abena (WHO Regional Office for Africa); Pedro Avedillo (WHO Regional Office for the Americas); Vineet Bhatia (WHO Regional Office for South-East Asia); Askar Yedilbayev (WHO Regional Office for Europe); Martin van den Boom (WHO Regional Office for the Eastern Mediterranean); and Kyung Hyun Oh (WHO Regional Office for the Western Pacific).

Others

The following participated as observers at the GDG meeting: Sevim Ahmedov (US Agency for International Development (USAID), USA); Andrew Burke, Frances Garden, Tasnim Hasan, Thomas Lung and Thu Anh Nguyen (University of Sydney, Australia); Sapna Bamrah Morris and Anand Date (US Centers for Disease Control and Prevention, USA); Siobhan Carroll (McGill University, Canada); Jacob Creswell (Stop TB Partnership, Switzerland); Celeste Gracia Edwards (The Global Fund, Switzerland); Agnes Gebhard (KNCV Tuberculosis Foundation, Kingdom of the Netherlands); Diana Gibb, Yohhei Hamada and Molebogeng (Lele) Rangaka (University College London, United Kingdom); Kobto Koura (International Union Against Tuberculosis and Lung Disease, France); Simon H. Schaaf (Stellenbosch University, South Africa); Cherise Scott (UNITAID, Switzerland); and Giorgia Sulis (University of Ottawa, Canada).

WHO acknowledges the contribution of the Guideline Review Committee in reviewing and approving the guidelines before their publication.

Funding

Production of the *WHO consolidated guidelines on tuberculosis. Module 1: Prevention – tuberculosis preventive treatment, second edition* was funded by grants to WHO from USAID, the US Centers for Disease Control and Prevention and Unitaid.

Recommendations for tuberculosis preventive treatment, 2020 update

Guideline Development Group

The GDG of the 2020 update of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* was composed of Mohammed Al Lawati (consultant physician, Oman); Helen Ayles (Infectious Diseases and International Health, London School of Hygiene and Tropical Medicine, Zambia); Rolando Cedillos (Service of Infectious Diseases and Integrated Programme for STI/HIV/AIDS, El Salvador);

Padmapriyadarsini Chandrasekaran (National Institute for Research in Tuberculosis, India); Diana Gibb (Medical Research Council, United Kingdom); Yohhei Hamada (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Japan); Anthony D. Harries (International Union Against Tuberculosis and Lung Disease, France; and London School of Hygiene and Tropical Medicine, London, Uniyed Kingdom); Alexander Kay (Baylor College of Medicine, Global TB Program, Eswatini); Nasehi Mahshid (Department of TB and Leprosy Control, Centre for Control of Communicable Diseases, Ministry of Health and Medical Education, Islamic Republic of Iran); Alberto Matteelli (University of Brescia, WHO Collaborative Centre for TB/HIV and TB Elimination, Italy); Lindiwe Mvusi (National Department of Health, South Africa); Kuldeep Singh Sachdeva (National Tuberculosis Elimination Programme, India); Nandi Siegfried (Medical Research Council / University of Cape Town, South Africa); Ezio Távora dos Santos Filho (WHO Civil Society Task Force member, Brazil); Marieke van der Werf (European Centre for Disease Prevention and Control, Sweden); Wim Vandevelde (Global TB Community Advisory Board, South Africa); and Irina Vasilyeva (Ministry of Health, Russian Federation). The co-chairs of the GDG were Lindiwe Mvusi and Nandi Siegfried. Dr Siegfried was also the GRADE methodologist

External reviewers

The External Review Group (ERG) was composed of Connie Erkens (KNCV TB Foundation, Kingdom of the Netherlands); Steve Graham (Center for International Child Health University of Melbourne, Australia); Giovanni B. Migliori (Maugeri Research Centre, Italy); Rohit Sarin (National Institute of TB and Respiratory Diseases, India); James Seddon (Imperial College London, United Kingdom); Alena Skrahina (Republican Scientific and Practical Centre for Pulmonology and TB, Belarus); and Carrie Tudor (International Council of Nurses, South Africa). Edits to the draft guidelines were also provided by people who responded to the call for public review on 1 July 2019.

Evidence reviewers

The following people contributed to the reviews and summarization of evidence for the guidelines:

Mayara Bastos, Jonathon Campbell and Richard Menzies (McGill University, Canada) provided the first draft of estimates and footnotes for the GRADE summary of evidence table from the trials of 4 months of daily rifampicin (PICO 6).

Richard Chaisson and Ritesh Ramchandani (Johns Hopkins University, USA) and Susan Swindells (University of Nebraska Medical Center, USA) provided the first draft of estimates and footnotes for the GRADE summary of evidence table from the BRIEF-TB/A5279 trial of 1 month of daily rifapentine and isoniazid (PICO 7).

Yohhei Hamada (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Japan) researched and wrote the report on the systematic review and meta-analysis of the safety of isoniazid preventive treatment in pregnancy (PICO 9), with support from Carmen Figueroa (WHO Global Tuberculosis Programme) and Mario Sánchez (WHO Management of Non-communicable Diseases, Disability, Violence & Injury Prevention). Lynne M. Mofenson (Consultant, WHO HIV Department) contributed a qualitative review of the safety of isoniazid in pregnancy. Amita Gupta and Nicole Salazar-Austin (Johns Hopkins University, USA) provided unpublished information from their studies to complete the evidence review.

WHO Guideline Steering Group

The WHO Guideline Steering Group was composed of Annabel Baddeley, Annemieke Brands, Dennis Falzon, Carmen Figueroa, Medea Gegia, Christopher Gilpin, Philippe Glaziou, Avinash Kanchar and Matteo Zignol (WHO Global Tuberculosis Programme); Françoise Renaud and Satvinder Singh (WHO Department of HIV/AIDS); Andreas Reis (Department of Information, Evidence and Research); and Lorenzo Moja (Department of Essential Medicines and Health Products). Wilson Were (WHO Department of Maternal, Newborn, Child and Adolescent Health) also reviewed the guidelines.

Others

The following people participated as observers at the GDG meetings: Sevim Ahmedov (US Agency for International Development (USAID), USA); Draurio Barreira Cravo Neto (Unitaid, Switzerland); Anand Date (Centers for Disease Control and Prevention, USA); Lucia Gonzalez Fernandez (International AIDS Society, Switzerland); Harry Hausler (TBHIV Care, South Africa); Cecily Miller (University of California San Francisco, USA); Surbhi Modi (Centers for Disease Control and Prevention, USA); Suvanand Sahu (Stop TB Partnership, Switzerland); Anna Scardigli (Global Fund to Fight AIDS, TB and Malaria, Switzerland).

WHO acknowledges the contributions of the Guideline Review Committee and its WHO secretariat in reviewing and approving the guidelines before their publication.

Funding

The 2020 update of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* was funded by grants provided to WHO by the US Agency for International Development (USAID) and the Russian Federation.

Abbreviations and acronyms

1HP	1 month of daily rifapentine plus isoniazid
3HP	3 months of weekly rifapentine plus isoniazid
3HR	3 months of daily rifampicin plus isoniazid
4R	4 months of daily rifampicin monotherapy
6H	6 months of daily isoniazid monotherapy
6Lfx	6 months of daily levofloxacin
9H	9 months of daily isoniazid monotherapy
ART	antiretroviral treatment
BCG	bacille Calmette-Guérin (vaccine)
CAD	computer aided detection
CI	confidence interval
CRP	C-reactive protein
CXR	chest radiography
ERG	external review group
GDG	Guideline Development Group
GRADE	grading of recommendations assessment, development and evaluation
IGRA	interferon-γ release assay
IPT	isoniazid preventive treatment (or monotherapy)
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
mWRD	molecular WHO-recommended rapid diagnostic test
OR	odds ratio
PICO	population, intervention, comparator and outcomes
PMTPT	programmatic management of tuberculosis preventive treatment
RCT	randomized controlled trial
RR	relative risk
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
TBI	tuberculosis infection
TBST	*M. tuberculosis* antigen-based skin test for TB infection
TNF	tumour necrosis factor
TPT	TB preventive treatment
TST	tuberculin skin test
USA	United States of America
USAID	US Agency for International Development
W4SS	WHO-recommended four-symptom screen
WHO	World Health Organization

Definitions

Note: The definitions listed below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

Active case finding (ACF): is synonymous with systematic screening for tuberculosis (TB) disease, although usually implemented outside a health facility.

Adolescent: is a person aged 10–19 years.

Adult: is a person aged > 19 years.

Bacteriologically confirmed TB: refers to TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved rapid diagnostic test such as Xpert® MTB/RIF or a urinary lipoarabinomannan assay.

Child: is a person aged < 10 years.

Contact: is any person who has been exposed to a person with TB disease.

Contact investigation: refers to the systematic identification of previously undiagnosed TB disease and TB infection (TBI) among the contacts of an index person and/or in settings where transmission occurs. Includes clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (TPT) (for those without TB disease).

High TB transmission setting: refers to a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission. TB patients are most infectious when they are untreated or inadequately treated. Transmission will be increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

Household contact: is a person who shared the same enclosed living space as the index person for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment.

Index person with TB: is the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index person is the one on whom a contact investigation is centred but is not necessarily the source.

Infant: is a child aged < 1 year (12 months).

People who use drugs: are those who engage in harmful or hazardous use of psychoactive substances, which could negatively affect their health, social life, resources and legal situation.

Programmatic management of TB preventive treatment (PMTPT): refers to all coordinated activities by public and private health caregivers and the community for providing TPT to people who need it.

Skin test: refers to the intradermal inoculation of either tuberculin (TST) or *M. tuberculosis* antigen (TBST) to elicit a response indicative of TBI.

TB preventive treatment (TPT): is treatment offered to individuals who are considered to be harbouring TBI and to be at risk of developing TB disease in order to reduce that risk. Also referred to as treatment of LTBI or TB infection, or TB preventive therapy.

Tuberculosis (TB): is the disease state due to *M. tuberculosis*. In this document, it is referred to as "TB disease" in order to distinguish it from "TB infection".

Tuberculosis infection (TBI): is a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no clinically manifest TB disease. Most infected people have no signs or symptoms of TB but are at risk of TB disease. TBI was previously referred to as "latent TB infection" or LTBI, but, as infection cannot always be considered latent, the term TBI (TBI) is preferred. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans.

Underweight: in people ≥ 19 years, usually refers to a body mass index < 18.5 kg/m^2; in people aged < 19 years, refers to a weight-for-age < –2 z-scores.

Executive summary

Tuberculosis infection (TBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease. It is estimated that about one fourth of the world's population has been infected with TB. TB preventive treatment (TPT) is one of the key interventions recommended by WHO to achieve the End TB Strategy targets, as upheld by the United Nations High-level Meeting on TB in September 2023. TPT fits within a larger framework of preventive actions envisaged in pillars 1 and 2 of the End TB Strategy, including screening for TB disease, infection control, prevention and care of people with HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation.

WHO guidelines on TPT account for the probability of progression to TB disease in specific risk groups, the epidemiology and burden of TB and the likelihood of a broad public health benefit of treatment. The main target readership of these guidelines is staff in ministries of health, other policy-makers working on TB, HIV, infectious diseases and maternal and child health and technical partners who support national programmes. This second edition of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* builds on and supersedes previous WHO guidance on the programmatic management of TB preventive treatment (PMTPT). Its main objectives are to include the latest evidence in its recommendations, particularly on TPT for individuals exposed to multidrug- or rifampicin-resistant TB (MDR/RR-TB) and to update recommendations on systematic TB screening and testing for TB infection (TBI). Some of the text of the recommendations has been revised to improve their clarity (Box 1).

Box 1. Main changes to the guidance in the current update (see also Annex 1)

- The recommendation on TPT for MDR/RR-TB was updated to align it with the relevant population, intervention, comparator and outcomes (PICO) and evidence reviewed by the guideline development group (GDG) in December 2023.
- Two recommendations on TB symptom screening in adults and adolescents with HIV were merged to integrate implementation of screening with TPT.
- One recommendation was added on use of new *M. tuberculosis* antigen-based tests for TBI published by WHO in 2022.
- Three recommendations on use of newly recommended screening tools and two recommendations on TB screening for household contacts and other risk groups were added from the 2021 WHO TB screening guidelines.
- One recommendation on TPT regimens was divided into two: one for regimens that are strongly recommended and the other for alternative regimen options that are conditionally recommended.
- Two recommendations that were outdated or were difficult to interpret were withdrawn and replaced by comments in the text. One was a recommendation against systematic testing and treatment of TBI in people with diabetes, people who use alcohol, tobacco smokers and underweight people; and the other was on provision of 36 months of isoniazid to people with HIV in high TB transmission settings.
- The text of nine recommendations was edited to reflect current terminology.
- The algorithm for management of TPT in contacts, people with HIV and other risk groups was revised to reflect new options for screening and testing for TBI.
- The TPT regimen drug dosage table was removed and will now appear only in the second edition of the *WHO operational handbook on tuberculosis preventive treatment*.
- The content of the guidelines was updated with recent references and the latest evidence, including on co-administration of rifapentine with dolutegravir and the safety of rifapentine and levofloxacin.
- The research gaps were updated to reflect the latest evidence reviewed.
- The annexes were updated with additions and modifications.

This second edition of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* was prepared in accordance with the requirements of the WHO Guideline Review Committee. The GDGs considered the certainty of the latest available evidence on effectiveness and harms and of evidence, values and preferences and issues of equity, resource use, acceptability and feasibility of implementation when updating or formulating recommendations and determining their strength. The GDG considered the implications of the best available evidence for each population subgroup at risk, the likelihood of progression from infection to TB disease of each group, and the incidence of TB disease as compared with that in the general population. The GDG used the guiding principle that individual benefit outweighs risk when recommending testing for TBI and TPT. TBI testing is desirable whenever feasible to identify people at highest risk of developing TB. Tools such as chest radiography (CXR) with computer aided detection (CAD) software, C-reactive protein (CRP) and WHO recommended rapid molecular diagnostic tests (mWRD) should be used to rule out TB disease before TPT is started. A requirement for additional resources to implement the guidance should not be viewed as a barrier but should stimulate programmatic mobilization of an appropriate level of funding.

The 21 recommendations in this edition of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* cover the critical steps in PMTPT and the cascade of preventive care: identification of populations at risk (people with HIV as part of the HIV care package, household contacts and others), TB screening and ruling out TB disease, testing for TBI, providing treatment and support, managing adverse drug reactions and monitoring adverse events, adherence and completion of treatment (Table 1). Most of the recommendations from the 2020 version are largely unchanged. The changes introduced are mainly inclusion of 6 months of daily levofloxacin (6Lfx) as a TPT option for people exposed to MDR/RR-TB in all settings, subject to certain conditions. Other recommendations relevant to PMTPT published in other WHO guidelines since 2020 are included. Operational limitations that require urgent action by countries in order to achieve global targets are highlighted. The new guidelines are accompanied by a second edition of the *WHO operational handbook on tuberculosis preventive treatment*, which contains practical details on programmatic implementation of the updated guidance. The two publications are being issued as components of the six-module series of WHO consolidated guidelines and operational handbooks, which cover all aspects of TB prevention and care. Both documents will be published on the WHO TB Knowledge Sharing Platform (https://extranet.who.int/tbknowledge).

Table 1. Recommendations in the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment*[a]

1.1. Identifying populations for TB preventive treatment
People with HIV
1. Adults and adolescents living with HIV who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if testing for TB infection is unavailable.
2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.
3. Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.

Household contacts of people with TB (regardless of HIV status)
5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if testing for TB infection is unavailable.
6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.
Other people at risk
7. People who are initiating anti-tumour-necrosis factor treatment, receiving dialysis, preparing for an organ or haematological transplant or have silicosis should be systematically tested and treated for TB infection.
8. Systematic testing and treatment for TB infection may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.
1.2. TB screening and ruling out TB disease
9. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.
10. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease. Those who report any of these symptoms may have TB, should be evaluated for TB disease and other diseases and should be offered TB preventive treatment if TB disease is excluded, regardless of their antiretroviral treatment status.
11. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease.
12. Among adults and adolescents living with HIV, C-reactive protein at a cut-off of > 5 mg/L may be used to screen for TB disease.
13. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease.
14. Among HIV-negative household contacts aged ≥ 5 years and other risk groups, the absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out TB disease before TB preventive treatment.
15. Among individuals aged ≥ 15 years in populations in which TB screening is recommended, systematic screening for TB disease may be conducted with a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination.
16. Among individuals < 15 years who are close contacts of a person with TB, systematic screening for TB disease should be conducted with a symptom screen of any one of cough, fever or poor weight gain; or chest radiography; or both.

1.3. Testing for TB infection

17. Either a tuberculin skin test (TST) or interferon-γ release assay (IGRA) can be used to test for TB infection.

18. *Mycobacterium tuberculosis* antigen-based skin tests (TBST) may be used to test for TB infection.

1.4. TB preventive treatment options

TB preventive treatment with isoniazid or rifamycins

19. The following TB preventive treatment options are recommended regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin.

20. The following alternative TB preventive treatment options may be used regardless of HIV status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin.

TB preventive treatment with levofloxacin

21. In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, 6 months of daily levofloxacin should be used as TB preventive treatment.

[a] The recommendations in the current update are compared with those in the 2020 guidelines in Annex 1.

Introduction

Background

Tuberculosis infection (TBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease *(1)*. As there is no "gold standard" test for TBI, the global burden is not known with certainty; however, about one fourth of the world's population is estimated to have been infected with *M. tuberculosis (2,3)*. The vast majority of people with TBI have no signs or symptoms of TB disease and are not infectious, although they are at risk of developing TB disease and becoming infectious. Several studies have shown that, in recent decades, an average 5–10% of people who are infected will develop TB disease over the course of their lives, usually within the first 5 years after initial infection *(4,5)*. The risk for TB disease after infection depends on several factors, the most important being immunological status *(1)*. At the second United Nations high-level meeting on TB in 2023, Member States committed themselves to providing TPT to at least 45 million people between 2024 and 2027 *(6)*.

TPT is a critical component of the WHO End TB Strategy and of other work to eliminate TB *(7–9)*. The efficacy of currently available TPT regimens ranges from 60% to 90% *(1)*. The potential benefit of treatment should, however, be carefully balanced against the risk of drug-related adverse events. Mass, population-wide testing and treatment of TBI are not feasible at present because the tests are imperfect, there is a risk of serious, potentially fatal adverse drug reactions, and the cost would be high, thus providing unclear benefit for populations at lower risk. The benefits of TPT are more likely to outweigh harm in infected individuals in population groups in whom the risk for progression to TB disease substantially exceeds that of the general population. In people exposed to MDR/RR-TB, which is more difficult to treat than drug-susceptible TB, provision of suitable TPT may be more justifiable. Programmatic management of TPT (PMTPT) involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those who start a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation. PMTPT fits within a larger framework of preventive actions envisaged in pillars 1 and 2 of the End TB Strategy, from screening for TB disease, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation.

Rationale

WHO guidelines on TPT are premised on the probability that TBI will progress to TB disease in specific risk groups, on the underlying epidemiology and burden of TB and on the feasibility and the public health benefit of the intervention. WHO global policy is expected to provide the basis for the development of national guidelines for PMTPT, adapted to local circumstances. These guidelines envisage a massive extension of TPT, including to individuals exposed to MDR/RR-TB, whereas global coverage of the intervention is still very low, even in priority target groups *(10)*. The 2020 edition of the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* was the first in the modular series of consolidated guidelines on various aspects of TB care, accompanied by operational handbooks. These documents were published on the WHO TB Knowledge Sharing Platform in 2021, and a training module with the same content was released in 2022 *(11)*. The 2024 edition of TPT guidelines and the associated operational handbook *(12)* will replace the earlier versions on the WHO TB Knowledge Sharing Platform.

Scope of the current update

The *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* include recommendations for the four milestones in the cascade of preventive care, namely identification of risk groups, TB screening and ruling out TB, testing for TBI, and choice and administration of the TPT regimen. The second edition of the TPT guidelines will have the same scope.

Since the previous update of the guidelines, in 2020, several developments have affected TPT policy. They include revision of WHO guidance on screening for TB disease and new modalities for testing for TBI *(13,14)*. In addition, two landmark trials of use of TPT for contacts of people with MDR-TB have been completed *(15,16)*. In the light of these new developments and continued demand from Member States for guidance on how best to protect people at risk of TB, the 2020 TPT guidelines were updated to ensure that the recommendations continue to be based on the latest available evidence.

The current update considered a review of evidence on one question, worded in PICO format[2]:

- Does TPT with levofloxacin improve outcomes in contacts exposed to MDR- or RR-TB as compared with other regimens or no treatment?

The methods used by the expert groups and evidence retrieval are further described in annexes 2–5. In making decisions on the wording and strength of the recommendation, the GDG considered the evidence not only for the effectiveness and safety of an intervention but also other dimensions important to both the people at risk and the programme, namely values, preferences, resource requirements, cost, impact on health equity, acceptability and feasibility, as is seen in the GRADE evidence-to-decision tables (Annex 4). A summary of unpublished data also used in formulating the new recommendation is provided in Annex 5 *(17,18)*.

Other changes made to the guidelines are summarized in Box 1. The recommendations in the second edition are compared with those in the 2020 guidelines in Annex 1.

Target readership

The second edition of the WHO guidelines on TPT provides a comprehensive set of recommendations for PMTPT for implementers of the WHO End TB Strategy and also for countries working towards TB elimination *(8,9)*. The guidelines are to be used primarily in national TB and HIV and maternal and child health programmes or their equivalents in ministries of health and by other policy-makers working on TB, HIV, infectious diseases and maternal and child health. They are also appropriate for staff of ministries of justice, correctional services and other government agencies that deliver health care, including prison, social and immigration services. The guidelines are also intended for clinicians in the public or the private sectors working on TB, HIV, infectious diseases, prevention, child health and noncommunicable diseases such as chronic kidney disease and cancer. The people directly affected by the guidelines are those in risk groups for whom TPT is recommended, namely people with HIV, contacts of people with TB and other people at increased risk of progression from TBI to disease in whom there is evidence of benefit of preventive treatment.

[2] Population, Intervention, Comparator and Outcome. See annexes 2 and 3 for a complete listing of PICOs and evidence summaries from guidelines since 2018.

1. Recommendations

1.1 Identifying populations for TB preventive treatment

Among individuals infected with *M. tuberculosis*, it is estimated that the average lifetime risk of progressing to TB disease is about 5–10% *(4)*. The risk is particularly elevated among children under 5 years and among people with compromised immunity *(1)*. As any treatment entails risk of harms and opportunity costs, TPT should be selectively targeted to population groups at highest risk of progression to TB disease, who would benefit most. When identifying populations at increased risk, consideration should be given to the epidemiology and pattern of TB transmission in the country, so that treatment is optimized to offer lasting protection. A comprehensive individual clinical assessment that considers the balance between the risks and benefits for the person receiving treatment is critical. This section describes recommendations for identifying population groups considered at highest risk of progression to disease and/or vulnerability to poor outcomes, namely people with HIV, contacts and other people at risk.

People with HIV

1. Adults and adolescents living with HIV who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if testing for TB infection is unavailable. *(Strong recommendation, high certainty of the estimates of effect)*

2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(Strong recommendation, moderate certainty of the estimates of effect)*

3. Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(Strong recommendation, low certainty of the estimates of effect)*

4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(Conditional recommendation, low certainty of the estimates of effect)*

Justification and evidence

TB is the most frequent cause of AIDS-related deaths worldwide, despite progress in access to antiretroviral treatment (ART) *(19)*. TB caused about 167 000 deaths among people with HIV in 2022, representing about one third of all HIV deaths *(10)*. Globally, people with HIV are about 18 times more likely to develop TB disease than those without HIV infection.

Recommendation 1, to give TPT to all people with HIV, was first published by WHO in 2011 *(20)*. A systematic review of 12 randomized controlled trials (RCTs) found that preventive treatment reduced the overall risk for TB by 33% (relative risk [RR] 0.67, 95% confidence interval [CI] 0.51; 0.87) among the 8578 people with HIV included in the trial *(21)*. For those who were tuberculin skin test (TST) positive, the reduction increased to 64% (RR 0.36, 95% CI 0.22; 0.61). Although not statistically significant, the reduction was 14% among TST-negative people (RR 0.86, 95% CI 0.59 ; 1.26) and those of unknown TST status (RR 0.86, 95% CI 0.48 ; 1.52). Most of the studies in the review were, however, conducted before ART became available, and there is now increasing evidence from observational studies and RCTs of the efficacy of TPT in people receiving ART. TB incidence has been reported to be high among all people with HIV who did not receive isoniazid preventive treatment (IPT), including those with a CD4 cell count > 350/mm^3 and who were TST negative *(22)*. A double-blinded RCT of 1329 people with HIV receiving ART found that the effect of IPT was not statistically significantly different between those who were positive or negative on TST or IGRA *(23)*. An RCT of 2056 people with HIV showed additive benefits of TPT plus ART in reducing both TB incidence and overall mortality *(24,25)*. Early initiation of ART and 6 months of IPT independently resulted in a risk of severe HIV-related illness that was 44% lower and a risk of death from any cause that was 35% lower than the risks with deferred initiation of ART and no IPT. The protective effect lasted for > 5 years.

The GDG at that time reviewed the evidence from the systematic reviews and discussed each population risk group identified for the prevalence of TBI, risk of progression to TB disease and the incidence of TB disease as compared with that in the general population. They concluded that the evidence shows a clear benefit of systematic testing and treatment of TBI for people with HIV. The wording of the current recommendation refers to TBI testing rather than TST as IGRA, and the new antigen-based skin tests (TBST) are alternative options (see **recommendations 17 and 18**). TPT should be given to adults and adolescents with HIV, regardless of their immune status and whether they are on ART, given the evidence of a protective effect additional to that of ART. A systematic review of studies conducted before ART became available showed the value of providing TPT immediately after successful completion of TB treatment among people with HIV in countries with a TB incidence > 100/100 000 population *(26,27)*. Since 2011, TPT has been recommended for children with HIV who were previously treated for TB (see next section). No evidence was found, however, for preventive treatment of people who had successfully completed treatment for MDR- or extensively drug-resistant TB. The effect of repeated courses of TPT is also unclear due to lack of evidence, and hence no recommendation was made *(28)*. The relative risk of TB transmission is determined by local authorities on the basis of risk of exposure (e.g. TB incidence, occurrence of undiagnosed or inadequately treated disease, population density, environmental factors) and host immune response *(29)*.

Pregnant women with HIV are at risk for TB, which can have severe consequences for both the mother and the fetus, with increased risks of maternal and infant death *(30)*. Pregnancy should not disqualify women with HIV from receiving TPT with medicines commonly used to treat TB disease that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin (classified as pregnancy category C by the US Food and Drug Administration *(31,32)*). Section 1.4 presents the position on use of TPT in pregnancy.

Recommendations 2–4 were first published by WHO in 2011 *(20)*. A systematic review conducted for establishing the original guidelines included two studies, both conducted in South Africa. One suggested a considerable reduction in mortality and protection against TB among HIV-infected children who received isoniazid for 6 months *(33)*. The other, however, showed no benefit of preventive treatment in infants in whom HIV infection was identified in the first 3–4 months of life, who had no known

exposure to TB disease and who were rapidly placed on ART and monitored carefully every month for new exposure to TB or emergence of TB disease *(34)*. Few RCTs included children on ART. In one trial of 167 children on ART, the incidence of TB was lower in those given TPT than in those who were not, but the difference was not statistically significant (incidence rate ratio 0.51, 95% CI 0.15; 1.75) *(35)*. A cohort study suggested an additive protective effect of TPT in children receiving ART *(36)*.

For infants with HIV aged < 12 months, the GDG recommended that TPT be given only to those who have a history of household contact with a person with TB and are considered not to have TB disease according to investigations conducted in line with national guidelines, because of limited data on the benefits. The GDG strongly recommended TPT for children aged ≥ 12 months with HIV but without clinical manifestations suggestive of TB disease, despite the low certainty of the evidence, because of the clear benefits seen in adults with HIV and the high risk for TB disease among people with HIV. Children ≥ 12 months with HIV who have clinical manifestations or who are contacts should be evaluated further and treated for TB disease or TBI as indicated (see also Fig. 1).

The GDG noted that, although the evidence for the efficacy of TPT in children on ART is limited, it is biologically plausible, given the evidence of additive effects in adults with HIV receiving ART. Thus, TPT is recommended for children, regardless of whether they are on ART or not.

Despite limited evidence on the value of TPT in children with HIV after successful completion of TB treatment *(20)*, the GDG considered that children with HIV who are at risk of reinfection could benefit from TPT. Therefore, the GDG conditionally recommended that all children with HIV who have been successfully treated for TB and are living in settings with high TB transmission as defined by national authorities (see also Definitions) may receive a course of TPT. This can be started immediately after the last dose of TB curative treatment or later, according to clinical judgement.

Household contacts of people with TB, regardless of HIV status

5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if testing for TB infection is unavailable. *(Strong recommendation, high certainty of the estimates of effect)*

6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(Conditional recommendation, low certainty of the estimates of effect)*

Justification and evidence

Recommendation 5 was initially published by WHO in 2015 and **recommendation 6** in 2018 *(17,37)*. A systematic review conducted for the 2015 guidelines on household contacts in countries with a TB incidence > 100/100 000 population was updated in 2018 *(37–39)* (see PICO 1 in Annex 3). The aim of the review was to determine the prevalence of TBI, progression to TB disease and the cumulative prevalence of TB among household contacts, stratified by age. Another 19 studies published between 2014 and 2016 were added. While the evidence reviewed related to HIV-negative child contacts, children with HIV who are household contacts of a person with bacteriologically confirmed pulmonary TB should also undergo investigation and treatment as necessary.

The prevalence of TBI was higher among adolescents aged > 15 years and adults than in children < 5 years, who were at greatest risk for progression to TB disease. In comparison with child household contacts < 5 years, the pooled risk ratios for progression to TB disease were lower in children

aged 5–15 years (0.28, 95% CI 0.12 ; 0.65, four studies) and for those aged > 15 years (0.22, 95% CI 0.08 ; 0.60, three studies). All household contacts, regardless of their age or TBI status, were at substantially higher risk for progression to TB disease than the general population (Table 2).

Table 2. Pooled estimates of risk for TB disease among household contacts stratified by age and baseline TBI status as compared with the general population

Age (years)	TBI-positive at baseline				Regardless of baseline TBI status			
	Follow-up < 12 months		Follow-up < 24 months		Follow-up < 12 months		Follow-up < 24 months	
	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio	No. of studies	Risk ratio
General population	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)
0–4	2	24.3 (0.73–81.0)	3	22.9 (7.7–68.6)	3	25.9 (16.9–39.7)	5	14.8 (9.8–22.3)
5–14	2	27.1 (17.5–54.1)	3	8.2 (2.3–29.4)	3	24.1 (16.9–34.4)	5	6.3 (2.9–13.7)
≥ 15	1	30.7 (17.5–54.1)	2	13.4 (9.5–18.8)	1	24.7 (14.2–43.0)	3	11.7 (7.6–18.0)

Both recommendations may apply to people with or without HIV. The GDG noted the significantly higher risk of infants and young children < 5 years for developing TB. Furthermore, the disease can develop rapidly in young children, and they are at greatest risk of severe and disseminated disease, which are associated with high morbidity and mortality. Therefore, the GDG strongly recommended TPT for child household contacts aged < 5 years, regardless of HIV status and background epidemiology of TB, but only after TB disease has been ruled out.

TPT is also conditionally recommended for household contacts in other age groups, according to clinical judgement on the balance between harm and benefit for individuals and the national and local epidemiology of TB, with special consideration of ongoing transmission of TB. In this group, confirmation of TBI with either IGRA or a skin test would be desirable (see section 1.3). With evidence of moderate to high certainty, the 2015 guidelines strongly recommended systematic testing and treatment of TBI in contacts, regardless of age, in countries with a TB incidence < 100/100 000 population *(37)*. In the 2020 update, the GDG considered that this recommendation could be applied in any country regardless of TB burden if tests for TBI and tests to rule out TB are available and reliable. Treatment may be justifiable without a TBI test after an assessment of the individual's risk of exposure and for development of TB disease in a given setting. The GDG noted that important considerations in implementation of these recommendations are the capacity of a caregiver to assess the intensity of exposure, the risks of infection and reinfection, the risk for developing TB disease and ascertainment of TBI by testing, as well as capacity to weigh the harm versus the benefit of treatment and the ability to exclude TB disease before initiation of treatment.

Other people at risk

7. People who are initiating anti-tumour-necrosis factor treatment, receiving dialysis, preparing for an organ or haematological transplant or who have silicosis should be systematically tested and treated for TB infection. *(Strong recommendation, low to very low certainty of the estimates of effect)*

8. Systematic testing and treatment for TB infection may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs. *(Conditional recommendation, low to very low certainty of the estimates of effect)*

Justification and evidence

Recommendations 7 and **8** were first published by WHO in 2015 *(37)*. The GDG considered evidence from three systematic reviews that were conducted for the previous guidelines on TBI to determine which of the 24 defined at-risk population groups should be prioritized for TBI testing and treatment *(37–39)*. Evidence of an increased prevalence of TBI, an increased risk of progression from TBI to TB disease and an increased incidence of TB disease was available for the following 15 risk groups: adult and child TB contacts, health-care workers and students, people with HIV, patients on dialysis, immigrants from countries with a high TB burden (incidence > 100 TB cases per 100 000 population), patients initiating anti-TNF therapy, people who use drugs, prisoners, homeless people, patients preparing for an organ or haematological transplant, patients with silicosis, patients with diabetes, people who engage in harmful use of alcohol, tobacco smokers and underweight people *(38)*. An increased risk for progression to TB was reported for 4 of the 15 groups: people with HIV, adult and child TB contacts, patients on dialysis and underweight people.

The GDG judged that people in clinical risk groups, such as patients initiating anti-TNF treatment, patients on dialysis, patients preparing for organ or haematological transplant and patients with silicosis *(40)*, would benefit most from testing for and treatment of TBI, regardless of the background TB epidemiology. The GDG considered that the benefit of TPT in reducing the risk of progression to disease would usually outweigh potential harm in these groups and made a strong recommendation despite low to very low certainty of the evidence.

The GDG concluded from the evidence that the benefits of systematic testing for TBI and TPT may not always outweigh the harm in health-care workers and students, immigrants from countries with a high TB burden, prisoners, homeless people and people who use drugs. The GDG judged, however, that the benefits are more likely to outweigh potential harm when the risks for reinfection are lower. In 2020, the GDG updated this recommendation to make it applicable to countries with both high and low TB prevalence on condition that a decision for systematic testing for TBI and offering TPT in these population groups be based on the local TB epidemiology and context, health infrastructure, capacity to exclude TB disease reliably, any adverse impact on health equity and overall health priorities. Greater benefit is expected for individuals who were recently infected with TB, as documented by conversion from a negative to a positive test of TBI (see section 1.3). The GDG also concluded that recent immigrants, particularly those from countries with a higher TB burden than that in the host country,[3] may be prioritized, especially within the first few years after entry.

Despite evidence for increased prevalence of TBI and disease in patients with diabetes, people who engage in harmful use of alcohol, tobacco smokers and underweight people, the GDG in 2014 noted the paucity of data from clinical trials on the benefits and harm of systematic testing and treatment of TBI. They concluded that systematic, routine testing and treatment of people with these risks alone might not always outweigh the potential harm, regardless of background TB epidemiology. In 2014, a recommendation against systematic testing and treatment of TBI in these four populations was issued

[3] Estimated rates of TB incidence in all countries are updated annually by WHO *(41)*.

due to the lower risk of progression from infection to disease than in the other at-risk populations listed above, in whom TPT was recommended. This was not based on direct evidence that TPT is harmful but was rather an attempt to prioritize TPT for populations at the highest risk of progression to disease. The recommendation was not intended to be construed as a blanket recommendation against any testing or treatment in these populations but rather for a case-by-case assessment of risk. Regrettably, the recommendation was often misinterpreted as meaning that diabetes, use of alcohol, tobacco smoking and underweight were contraindications for TPT in individuals who were otherwise eligible. Thus, in 2024, the GDG reconsidered its position and replaced the recommendation with a statement that no recommendation is possible for these subgroups, given the evidence. Trial evidence on TPT in people with diabetes is expected to become available for review in a few years' time *(42)*.

The GDG agreed that prioritization of groups according to their risk and the local and national context would be acceptable to people with TBI and to stakeholders such as clinicians and programme managers. It noted that the high risk for ongoing TB transmission in certain groups, such as front-line health-care workers (including students), prisoners (and prison staff), immigrants from areas with a higher TB burden than that in the host country, homeless people and people who use drugs, requires attention, so that the benefit of treatment is not compromised by subsequent reinfection. TPT complements other preventive components of the programme for active TB case-finding, infection control and early treatment of TB disease *(29)*.

Implementation considerations

In their normative and planning documents, national TB and HIV authorities and other stakeholders should clearly define priority populations for PMTPT. The aim should be to provide lasting protection from progression to TB disease to a maximum number of individuals at risk, thus limiting continued transmission and reinfection and reducing TB incidence over time. People with HIV and household contacts were the primary targets for global action by Member States at the United Nations high-level meetings in 2018 and 2023 *(6,43)*. The GDG stressed that the best available evidence should be used to ensure that the benefits outweigh the risks to individuals in these groups and to make the best possible use of resources, which could yield savings for the entire health-care system. Any additional resources necessary to implement the guidance should not be viewed as a barrier but should stimulate programmatic mobilization of more funding. The GDG noted the value of ART in preventing TB in people with HIV and urged countries to ensure universal access to ART, as per WHO policy *(44)*.

Provision of TPT for people with HIV should be a core component of the HIV package of care and should be the responsibility primarily of national HIV/AIDS programmes and HIV service providers *(44,45)*. Some household contacts and other people eligible for TPT (e.g. people receiving dialysis, prisoners) will also be HIV positive and would therefore require individual attention to minimize the likelihood of developing TB disease. Care should be coordinated with the health services responsible for TB. TPT should be viewed as one of a comprehensive set of interventions. Among people with HIV who were treated for TB in the past, TPT should be prioritized for adults and adolescents who have been re-exposed to TB.

In addition to HIV care, nutrition supplementation has been shown to reduce the risk of TB disease by 39–48% in household contacts who are undernourished *(46)*.

Confirmation of TBI with either IGRA or skin testing and reliable exclusion of TB disease with sensitive tests such as CXR are desirable before starting TPT. If these tests are not available, TPT should not be withheld from eligible people if TB disease has been excluded on clinical grounds alone (see section 1.2).

Identification of populations for TBI testing and TPT raises various ethical issues *(47,48)*. First, as TBI is an asymptomatic, non-contagious state, the ethical obligations are different from those for TB disease. For example, in the absence of an immediate risk of transmission, it would be unethical to restrict the movement of a person with TBI who refuses treatment. Lack of evidence of the benefit of systematic testing and treatment in certain populations (e.g. people with diabetes or who are

underweight) should not preclude offering preventive treatment to individuals with these conditions who are judged to be at increased risk of progression. Secondly, lack of tests for measuring individual risk for development of TB disease may complicate communication. Informed consent requires effective, adequate communication to each person about the uncertainty of current TBI tests to predict progression to TB disease, individual host variation and the protective benefit expected from treatment versus adverse reactions. Appropriate means to obtain informed consent should comply with international human rights standards and account for differences in language, literacy and legal status. Risk and uncertainty must be communicated in a way that is culturally and linguistically appropriate, including to people whose first language is not that of the local setting, to children and to people in prison. User feedback collected during screening programmes is useful for communication. Thirdly, TBI disproportionately affects individuals and groups that are already disadvantaged due to factors such as disease, socio-economic situation or legal status. Efforts must be made to address any inequity in access to services and to uphold human rights, so that the vulnerability of target groups does not impede their access to screening and treatment or violate their rights. Any intervention for vulnerable groups, including people in prisons and children, should include measures to minimize the risk of stigmatization, such as protecting confidentiality of personal data and informed consent. The GDG emphasized that a person's status – positive for TBI or receiving TPT – should not affect any immigration procedure or entry to the host country, and this should be reflected in laws or other regulations. People should be tested for TBI and receive TPT in strict adherence to human rights and ethical considerations *(49)*. Policies should be evaluated by users from an ethical perspective and the views and experiences of affected populations collected after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant *(50)*. Person-centred TBI care includes equitable provision, with no added disadvantage for marginalized and vulnerable populations, and emphasizes the human rights aspects of TPT so that appropriate safeguards are included in law, policy and practice to minimize any additional stigmatization, discrimination, violation of bodily integrity or restrictions on freedom of movement. In person-centred TBI care, people who are offered testing and treatment must understand the uncertainties, so that they can participate in care options. These guiding principles are based on established principles of human rights such as consent, non-coercion and confidentiality *(48)*.

1.2 TB screening and ruling out TB disease

Giving TPT to someone who has TB disease can delay resolution of disease and favour the emergence of drug resistance. Excluding TB disease before initiating preventive treatment is one of the critical steps in the TBI care pathway. This section proposes approaches for ruling out TB disease and diagnosing TBI in people at risk of TB according to HIV status, symptoms, household contact, other risk factors, age, TBI test results and abnormality on CXR (Fig. 1). The evidence and the recommendations for these steps are briefly discussed, as are tools for TB screening, first recommended in 2021 *(13)*.

People with HIV

9. Infants and children living with HIV who have poor weight gain,[4] fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age. *(Strong recommendation, low certainty of the estimates of effect)*

10. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease. Those who report any of these symptoms may have TB, should be evaluated for TB and other diseases and should be offered TB preventive treatment if TB disease is excluded, regardless of their antiretroviral treatment status. *(Strong recommendation, moderate certainty of the estimates of effect)*

11. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease. *(Conditional recommendation, low certainty of the estimates of effect)*

12. Among adults and adolescents living with HIV, C-reactive protein at a cut-off of > 5 mg/L may be used to screen for TB disease *(Conditional recommendation, low certainty in the estimates of effect)*

13. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease. *(Conditional recommendation, moderate certainty in the estimates of effect)*

Justification and evidence

A systematic review of studies on infants and children, conducted for the 2011 guidelines provided limited evidence on the best approach to screening *(26)*. Using these few studies and expert opinion, the previous GDG recommended a screening rule of poor weight gain, fever, current cough and a history of contact with a person with TB (**recommendation 9**). A systematic review was undertaken for the 2018 update to assess the performance of the screening rule; however, the only publication found was of a study of 168 children aged ≤ 12 years hospitalized with HIV in Kenya *(51)*. In this study, the sensitivity was 100% (95% CI, 94 ; 100.0) and the specificity was 5% (95% CI, 1 ; 11). The systematic review conducted for the 2021 TB screening guidelines comprised two studies conducted in outpatient settings, with a total of 20 926 participants *(13)*. In this review, the combined symptom screen (in which the presence of any symptom constituted a positive screen) had a pooled sensitivity of 61% (95% CI 58% ; 64%) and a pooled specificity of 94% (95% CI 86% ; 98%) (Table 3). Despite the lack of high-certainty evidence, the GDG considered that a strong recommendation for symptom screening was warranted for children < 10 years who were living with HIV, given the high risk of disease and of mortality when the diagnosis is missed and TB is left untreated.

Infants and children with HIV should be screened for TB as part of standard, routine clinical care, regardless of whether they are receiving TPT or ART. Symptom-based screening is generally acceptable to caregivers and people and is feasible even in resource-limited settings. Therefore, the GDG decided to make a strong recommendation for use of symptom screening in children with HIV. TB disease should be ruled out for those who have one or more symptoms. The GDG also noted that clinicians should broaden the differential diagnosis to include other diseases that may cause current cough, fever and poor weight gain in children with HIV. If the evaluation shows no signs of TB disease and the clinician

[4] *Poor weight gain* here is defined as reported weight loss, very low weight-for-age (< –3 Z-scores), underweight (weight-for-age < –2 Z-scores), confirmed weight loss (> 5%) since the last visit or growth curve flattening

decides not to treat for TB disease, children with HIV should be offered TPT, regardless of their age. Infants < 12 months of age should, however, be given TPT only if they have a history of household contact with a person with TB and TB disease has been excluded according to national guidelines. Guidance on further testing for TB in people with HIV who have suggestive clinical features is available elsewhere *(44)*.

The text of **recommendation 10** is a combination of two related recommendations in the 2015 guidelines that were updated in 2018 *(17,37)*. In 2011, WHO conducted a systematic review and a meta-analysis of data for individual patients and recommended a symptom-screening rule of a combination of current cough, weight loss, night sweats and fever to exclude TB disease in adults and adolescents *(52)*. The review showed that the rule had a sensitivity of 79%, a specificity of 50% and a negative predictive value of 97.7% at a TB prevalence of 5%. Most of the people with HIV in the studies included in the systematic review were not receiving ART.

During the 2018 updating of the guidelines, a systematic review was undertaken to compare the performance of the four-symptom screen in people with HIV who were and were not receiving ART (see PICOs 2 and 3 in Annex 3 and Table 2 in *(53)*). Data from 17 studies were used in the analysis. The pooled sensitivity of the four-symptom screen for people with HIV on ART was 51.0% (95% CI 28.4 ; 73.2), and the specificity was 70.7% (95% CI 47.7 ; 86.4); in people with HIV who were not receiving ART, the pooled sensitivity was 89.3% (95% CI 82.6 ; 93.6), and the specificity was 27.2% (95% CI 17.3 ; 40.0). In two studies on addition of abnormal CXR findings to the screening rule for people with HIV on ART *(54,55)*, the pooled sensitivity was higher (84.6%, 95% CI 69.7 ; 92.9), but the specificity was lower (29.8%, 95% CI 26.3 ; 33.6) than for the symptom screen alone. In all studies, the median prevalence of TB among people with HIV on ART was 1.5% (interquartile range, 0.6–3.5%). At a 1% prevalence of TB, the negative predictive value of the symptom screening rule was 99.3%; addition of abnormal CXR findings increased the negative predictive value by 0.2%. No studies of the addition of CXR to the symptom rule for pregnant women were found. The GDG agreed that, in adults and adolescents with HIV, the four-symptom screen (current cough, fever, weight loss or night sweats) is useful for ruling out TB disease, regardless of ART use, although confirmation of TBI with IGRA, TST or TBST would be desirable before starting TPT. It noted the potential benefits of adding normal CXR findings to the rule, while recognizing that the improvement in performance was marginal. Moreover, increased use of CXR would add more false-positive results to the screening rule, which would require more investigations for TB and other illnesses. Therefore, the GDG reiterated that CXR may be added as an additional investigation only if it does not pose a barrier to the provision of preventive treatment for people with HIV. It should not be a requirement for initiating TPT. Although no study was found of the effect of adding CXR in testing pregnant women, the GDG noted that pregnant women with HIV could also benefit, as long as good practices are observed to prevent harmful exposure of the fetus to radiation *(56)*.

In 2020, a systematic literature review and meta-analysis of individual data on patients were conducted to assess further the accuracy of the WHO-recommended four-symptom screen (W4SS) of people with HIV and of important subgroups and to identify other screening tools and strategies to increase detection of TB in people with HIV *(13)*. The screening tools and strategies reviewed by the GDG included CRP, CXR and mWRD, as both stand-alone tests and in combination with the W4SS. Culture was the reference standard for assessing the accuracy of the screening strategies (Table 3). The meta-analysis of data on individual patients comprised 23 studies of 16 269 participants with HIV, in which the accuracy of the W4SS was reviewed. Most of the studies addressed pulmonary TB disease.

The W4SS has suboptimal accuracy for some subgroups of people with HIV. The specificity is low, 37–38%, among all people with HIV and even lower among people newly enrolled or not on ART. Therefore, people who do not have TB disease are frequently screened as positive and are referred unnecessarily for diagnostic evaluation. This reduces the efficiency of screening programmes (e.g. with higher costs for diagnostic testing) and slows initiation of TPT. The sensitivity of W4SS is also low (53%) among people with HIV on ART; thus, almost half of prevalent TB cases are not identified in routine symptom screening alone. In a setting in which the prevalence of TB is 1%, 742 of 1000 outpatients screened with the W4SS and CRP would be true negatives and eligible for TPT, while only 416 would be found to be eligible with the W4SS alone. Restricted access to CRP or CXR should not be a barrier to initiating TPT.

Table 3. Diagnostic accuracy of screening tests in people with HIV

Population	W4SS		C-Reactive protein Cut off > 5–10 mg/L		CXR		mWRDs	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
All people with HIV	83%	38%	90%/83%	50%/65%	93%	20%	69%	98%
Outpatients on ART	53%	70%	40%/20%	80%/90%	85%	33%	54%	99%
Outpatients not on ART	84%	37%	89%/82%	54%/67%	94%	19%	72%	98%
≤ 200 CD4 cells/μL	86%	30%	93%/90%	40%/54%	94%	14%	76%	97%

CD4, Cluster of differentiation 4; CXR, chest X-ray; mWRDs, molecular WHO-recommended rapid diagnostic test; W4SS, WHO-recommended four-symptom screen

Note: The estimates of accuracy are independent for each test. The negative predictive value of all of the above screening tests in populations with a TB prevalence of 0.5–2% is ≥ 99%.

Recommendation 11 on use of CXR for people with HIV was first made in 2018 to update the position in the 2011 guidelines *(26)*. Since 2021, WHO has also conditionally recommended use of CAD software programmes to interpret digital CXRs for pulmonary TB during screening and triage of people aged ≥ 15 years, regardless of HIV status *(13)*.

Use of CXR for screening in parallel with symptom screening improves the sensitivity over that with the W4SS alone in all subgroups of people with HIV. In particular, screening with CXR significantly improves the sensitivity in people with HIV who are on ART and is the most sensitive screening strategy for this group. When available, CXR is recommended for use in parallel with the W4SS to rule out TB disease before initiating TPT in people with HIV who are on ART *(13)*. The evidence on the performance of CXR and the W4SS for all people with HIV reviewed before making the 2021 TB screening guidelines was from eight studies, conducted in Benin, Botswana, Brazil, Guinea, India, Kenya, Malawi, Myanmar, Peru, South Africa and Zimbabwe, with a total of 6238 participants (Table 3). CXR alone was found to have similar sensitivity to and similar or higher specificity than the W4SS in all subpopulations. When CXR was conducted after a positive W4SS, CXR was less or similarly sensitive and more or similarly specific. When CXR was used in parallel with the W4SS, the sensitivity was higher or similar and the specificity was similar.

Recommendation 12 relates to the use of CRP for screening adults and adolescents with HIV for TB disease. CRP is an indicator of general inflammation that can be measured with point-of-care tests in capillary blood collected by finger prick. The evidence reviewed comprised six studies conducted in Kenya, South Africa and Uganda with a total of 3971 participants *(13)*. The accuracy of CRP based on cut-off values of > 5 mg/L and > 10 mg/L as indicators of TB disease was reviewed, and the accuracy of two was considered to be similar or superior to that of the W4SS. The cut-off value of > 5 mg/L was recommended, as it is the lowest threshold for abnormality in many clinical settings and is more sensitive than the value of > 10 mg/L. The meta-analysis of data on individual patients on CRP with a cut-off of > 5 mg/L reported similar sensitivity and higher or similar specificity to the W4SS in all the subpopulations assessed (Table 3). When CRP was combined with the W4SS and used in parallel, it had similar or greater sensitivity and specificity than the W4SS alone in all populations, depending on the cut-off threshold used and the subpopulation assessed, while a positive screen with either tool led to a diagnostic test. CRP was found to be most accurate for outpatients who were not on ART as compared with the W4SS alone, which had a sensitivity of 84% (95% CI 75% ; 90%) and a specificity of 37% (95% CI 25% ; 50%) in this subpopulation. When performed sequentially after a positive W4SS in people with HIV who were not on ART, CRP with a cut-off of > 5 mg/L was as sensitive (84%; 95% CI 73% ; 90%) as the W4SS alone but was significantly more specific (64%; 95% CI 55 ; 72%). Like the W4SS, the specificity of CRP for TB screening in inpatients with HIV was extremely low, probably due to competing comorbidities that would also result in raised CRP levels and symptoms.

Recommendation 13 relates to use of mWRD for screening adults and adolescents with HIV for TB disease. A systematic review of the performance of mWRD in screening for TB among people with HIV comprised 14 studies with a total of 9209 participants. The Xpert MTB/RIF assay was the mWRD used in most of the studies. Use of an mWRD alone had a sensitivity of 69% (95% CI 60% ; 76%) and a specificity of 98% (95% CI 97% ; 99%) as compared with use of the W4SS followed by an mWRD, which had sensitivity of 62% (95% CI 56% ; 69%) and a specificity of 99% (95% CI 97% ; 99%) (Table 3). The accuracy of the mWRD was not significantly different from that of the W4SS followed by the mWRD in various subpopulations.

Household contacts of a person with TB and other risk groups

Infants and children < 5 years of age[5]

Justification and evidence

Symptom-based screening has been reported to be a safe, feasible contact management strategy in children, even in resource-limited settings *(58,59)*. Modelling of the parameters for a high TB burden setting suggested that provision of TPT without TBI testing is cost-effective for child contacts < 5 years *(60)*. See section 1.1 for the background of the recommendation for TBI testing and treatment in this risk group.

Evidence reviewed for the 2021 TB screening guidelines on the performance of symptom screening in children and adolescents < 15 years who are close contacts of a person with TB comprised four studies with a total of 2695 participants *(13)*. A comparison of a screen of symptoms including any one of cough, fever or poor weight gain, in which the presence of any symptom constitutes a positive screen, with a composite reference standard indicated a pooled sensitivity of 89% (95% CI 52% ; 98%) and a pooled specificity of 69% (95% CI 51% ; 83%) *(13)*. The evidence on the performance of CXR in close contacts < 15 years who were exposed to people with TB comprised four studies with a total of 2550 participants. In comparison with a composite reference standard, screening for abnormalities on CXR suggestive of TB had a pooled sensitivity of 84% (95% CI 70% ; 92%) and a pooled specificity of 91% (95% CI 90% ; 92%).

Household contacts aged ≥ 5 years and other risk groups

14. Among HIV-negative household contacts aged ≥ 5 years and other risk groups, the absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out TB disease before TB preventive treatment. *(Conditional recommendation, very low certainty of the estimates of effect)*

15. Among individuals aged ≥ 15 years in populations in which TB screening is recommended, systematic screening for TB disease may be conducted with a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination. *(Conditional recommendation, very low certainty of the estimates of effect)*

16. Among individuals < 15 years who are close contacts of a person with TB, systematic screening for TB disease should be conducted with a symptom screen of any one of cough, fever or poor weight gain; or chest radiography; or both. (*Strong recommendation, moderate to low certainty of the estimates of effect*).

Justification and evidence

Recommendation 14 for ruling out TB disease in contacts aged ≥ 5 years and other HIV-negative risk groups is conditional, due to the very low certainty of the evidence, which is from a study originally included in the 2018 guidelines *(17)*. The systematic review determined the sensitivity and specificity of screening based on symptoms and/or CXR for ruling out TB disease in HIV-negative people and people of unknown HIV status for the 2015 guidelines (see PICO 3 in Annex 3) *(61)*. To illustrate how the various screening and diagnostic algorithms are expected to rule out TB disease, a simple model was constructed to compare the following six screening criteria: (i) any TB symptom, (ii) any cough, (iii) cough for 2–3 weeks, (iv) CXR abnormality suggestive of TB, (v) any CXR abnormality and (vi) a

[5] For TBI testing and TPT in children < 5 years, see recommendations in section 1.1 and the algorithm in Fig. 1.

combination of any CXR abnormality or any TB symptom. The model indicated that the combination of any CXR abnormality and the presence of any symptoms suggestive of TB (i.e. cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) would have the highest sensitivity (100%) and negative predictive value (100%) for ruling out TB.

Before the 2018 guidelines update, the review was updated to include household contacts aged ≥ 5 years of people with pulmonary TB in high TB burden countries *(62)*. Seven studies of the accuracy of "any CXR abnormality" had a pooled sensitivity of 94.1% (95% CI 85.8 ; 97.7) and a pooled specificity 86.8% (95% CI 79.7 ; 91.7). In a hypothetical population of 10 000 HIV-negative individuals in a country with a TB prevalence of 2%, use only of any TB symptoms for screening would wrongly classify 54 people with TB as not having TB disease and being offered TPT. In contrast, use of any abnormal CXR finding would result in 12 people with TB being offered preventive treatment. Use of the combination of any TB symptoms plus any CXR abnormality would result in no people with TB disease being incorrectly offered preventive treatment. At a TB prevalence of 2%, use of any TB symptoms alone as the screening criterion would require investigations of 16 extra non-TB patients for every individual with TB identified, whereas use of any abnormal CXR finding would require TB investigation of 7 extra non-TB patients for every individual with TB identified. Use of the combination of any TB symptoms plus any CXR abnormal finding would increase the number of individuals requiring TB investigation to 15 extra non-TB patients for every individual with TB identified.

Recommendations 15 and **16** are related to use of symptom screen, CXR or mWRD, alone or in combination, to screen adults and adolescents for TB disease. A systematic review of the diagnostic accuracy of using symptoms and CXR to detect TB disease among individuals aged ≥ 15 years with negative or unknown HIV status was undertaken for the 2021 TB screening guidelines *(13)*. Table 4 shows that, overall, screening for cough has low sensitivity but higher specificity, while screening for any TB symptom improves the sensitivity but reduces the specificity. CXR is both highly sensitive and specific. mWRDs are less sensitive when used for screening than when they are used in diagnostic use but are very specific.

Table 4. Accuracy of tests in HIV-negative people aged ≥ 15 years in high-risk groups

Screening tool	Sensitivity	Specificity
Prolonged cough	42%	94%
Any cough	51%	88%
Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss)	71%	64%
CXR (any abnormality)	94%	89%
CXR (suggestive of TB)	85%	96%
mWRD	69%	99%

CXR, chest X-ray; mWRDs, molecular WHO-recommended rapid diagnostic test

The reference standard is culture.

In conclusion, a parallel screening algorithm based on any symptom of TB and any abnormal CXR finding is likely to be highly sensitive. Therefore, the absence of any TB symptoms and any CXR abnormality can be used to exclude pulmonary TB disease before initiating TPT among HIV-negative household contacts aged ≥ 5 years and in other risk groups. mWRDs may be useful when higher specificity is desirable, such as in situations of limited capacity for confirmatory testing after a positive screen.

The GDG reiterated that national guidelines should specify the investigations that are necessary to rule out TB disease. It noted that screening of child contacts could include testing for TBI (see section 1.3) and CXR, although, lack of those investigations should not be a barrier for either diagnosis of TB disease or provision of preventive treatment. In the absence of those tests, clinical assessment alone is sufficient to decide on initiation of TPT, particularly for household contacts aged < 5 years of a person with bacteriologically confirmed pulmonary TB.

The GDG concluded that symptom screening with or without the addition of CXR should be acceptable for individuals and programme managers. CXR could increase the confidence of health-care providers that TB disease has been ruled out and reduce concern that TPT is being administered inappropriately. The GDG for the 2021 WHO guideline on TB screening reviewed the evaluations of three CAD products used with digital CXR and concluded that CAD can be considered accurate when compared with human readers. The GDG therefore conditionally recommended its use for TB screening and triage in individuals aged ≥ 15 years *(13)*.

Implementation considerations

Fig. 1 presents an algorithm for testing for TBI and TPT, with separate entry points for people with HIV, household contacts and other people at risk for TBI. More detailed algorithms for screening and testing for TBI are available in the two handbooks *(63,64)*.

The W4SS is recommended for testing all people with HIV at every visit to a health facility or contact with a health worker to ensure early detection of TB disease. Other clinical features may also be helpful (e.g. poor weight gain in pregnant women and lymphadenopathy). People who have exclusively extrapulmonary TB may have clinical manifestations that are not necessarily pulmonary and may therefore require further evaluation before TB is definitively excluded. Other diseases that cause any of the four symptoms should be investigated in accordance with national guidelines and sound clinical practice. Individuals found not to have TB disease should then be assessed for TPT.

Where CXR or interpretation of radiography is not available, the absence of any TB symptoms alone can be considered sufficient before starting TPT. This would be the most sensitive of all the symptom-based screening rules, and its negative predictive value is high in most settings. Addition of abnormal CXR findings to the symptom screening rule would improve its sensitivity but also increase the logistics and infrastructure required, the cost to individuals and health services, and the requirement for qualified staff or the availability of CXR with CAD. The optimal frequency of CXR in regular TB screening of people with HIV is uncertain. Adding CXR to symptom screening at every visit would represent a significant burden on individuals and health systems. Local authorities should define its application and frequency according to their local epidemiology, health infrastructure and resources. Either CXR with CAD or radiologists or other trained health-care workers must be available to interpret CXR. mWRDs may be useful when greater specificity is desirable, such as when there is limited capacity for confirmatory testing after a positive screen.

The GDG noted that screening with CXR or mWRD should not be a prerequisite or a barrier to initiating TPT in people with HIV because additional resources are required, in view of the marginal gain in negative predictive value. Conversely, in people with HIV and a low CD4 count, TB disease may be present despite a normal CXR. People with HIV who have any of the four symptoms or abnormal CXR findings may have TB disease and should be investigated for TB and other diseases. Xpert® MTB/RIF should be used as the initial diagnostic test.

TPT should not be withheld from an asymptomatic individual at risk of infection if TBI testing and/or CXR is unavailable, as some people may have both risks (e.g. people with HIV who are also contacts of people with TB), in which case the triage shown in the figure would have to be adapted.

It is critical to ensure proper follow-up and evaluation for TB and other diseases in household contacts with abnormal CXR findings or TB symptoms. The investigations should be performed in accordance with national guidelines and sound clinical practice. Contacts found not to have TB disease should be assessed for TPT. Although TBI testing is not a requirement for initiating TPT, it may be done as a part of eligibility screening where feasible (see section 1.3).

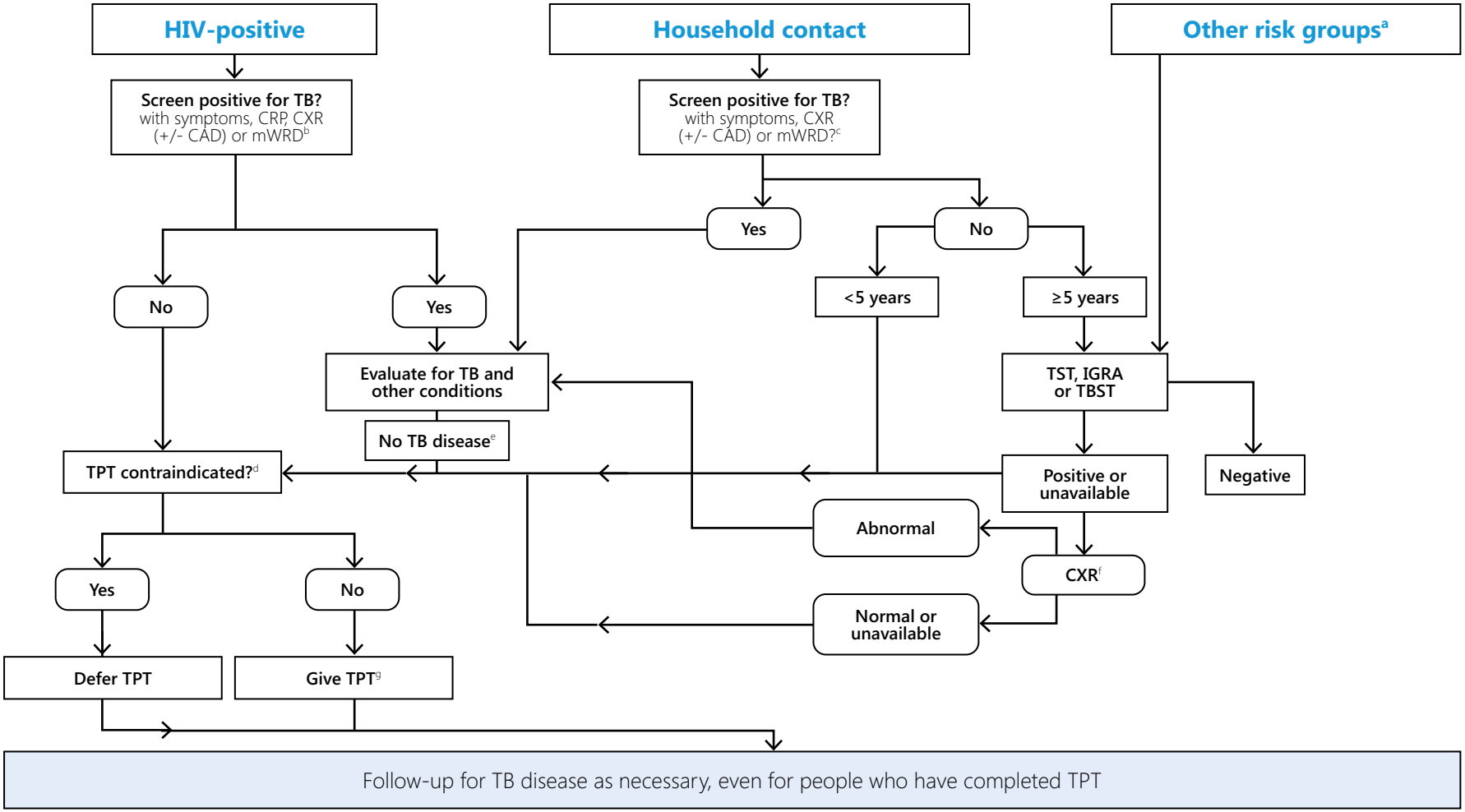
A previous history of TB or TPT should not be a contraindication for TPT in cases of re-exposure, after exclusion of reactivated disease. Such individuals, including those with fibrotic radiological lesions, may be at increased risk of progression *(65,66)*. The choice of TPT also depends on the presence of contraindications (e.g. active hepatitis or symptoms of peripheral neuropathy when isoniazid is considered) or the likelihood of drug–drug interactions, particularly when rifamycin regimes are being considered (see section 1.4).

Different symptom screening approaches have different sensitivity and specificity. The facility of symptom screening makes it a much more accessible programme option. Symptom screening is standard in a clinical workup and can be repeated as often as necessary. In contrast, additional resources are necessary for CXR and mWRDs. Scaling up mWRDs for diagnosis should be prioritized (if full access has not yet been achieved) before scaling it up for screening, as it requires significant resources, including increased capacity in and expansion of diagnostic and sample transport networks.

Countries should include the W4SS, CRP, CXR and mWRD in national TB screening algorithms according to their feasibility, the level of the health facility, resources and equity. While all four tools are recommended for people with HIV, CRP is particularly accurate for TB screening of people who are not yet receiving ART, and CXR enhances the sensitivity of the W4SS in people receiving ART, both of which might be considered when choosing algorithms. Consideration should also be given to the added benefit of including CRP for ruling out TB disease before initiating TPT among people with HIV.

CXR has been used to screen for TB for several decades. CXRs are also routinely used to triage people presenting for care who show signs, symptoms or risk factors for TB to determine the most appropriate clinical pathway for proper evaluation. In many settings, however, use of CXR for TB screening and triage for TB disease is limited by the paucity of health personnel trained to interpret radiographic images and by substantial intra- and inter-reader variation in its accuracy to detect abnormalities associated with TB *(13)*. CAD is useful in such situations.

Fig. 1. Combined algorithm for screening and testing individuals at risk before starting TB preventive treatment



CAD, computer aided detection of TB; CRP, C-reactive protein; CXR, chest radiography; IGRA, interferon-γ release assay; mWRD, molecular WHO-recommended rapid diagnostic test; TB, tuberculosis; TBST, *Mycobacterium tuberculosis* antigen-based skin test; TPT, TB preventive treatment; TST, tuberculin skin test.

[a] Including miners with silicosis, people on dialysis or anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines. TB disease should be ruled out for people in this category.

[b] For children aged ≥ 10 years, a four-symptom screen is used (current cough or fever or weight loss or night sweats). For children aged < 10 years, consider their history of contact with TB or reported or confirmed weight loss or growth curve flattening or weight for age < –2 Z-scores. Asymptomatic infants aged < 1 year with HIV are given TPT only if they are household contacts of people with TB. For other screening options, see the latest WHO guidance (TB-KSP).

[c] Any one of cough or fever or night sweats or haemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children, poor weight gain (plateau on growth chart), reduced playfulness or lethargy should also be included in symptom screening; cough may be absent. For other screening options see the latest WHO guidance (TB-KSP).

[d] Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications. The person is counselled about the benefits and potential risks of TPT.

[e] In household contacts aged ≥ 5 years, TST, IGRA or TBST is recommended before consideration of TPT.

[f] CXR is required only if it was not conducted at a previous step.

[g] Regimen chosen according to age, strain (drug susceptible or otherwise), risk of toxicity, availability and preference. Adherence supported until completion as prescribed.

1.3 Testing for TBI

Testing for TBI increases the certainty that individuals targeted for TPT will benefit better from it. There is, however, no gold standard test for diagnosing TBI. All the currently available tests – TST, IGRA and TBST – are indirect and require a competent immune response for a valid result. A positive test result by any one method is not by itself a reliable indicator of the risk of progression to TB disease. The evidence and the recommendations for TBI testing are discussed in this section.

17. Either a tuberculin skin test (TST) or interferon-γ release assay (IGRA) can be used to test for TB infection. *(Strong recommendation, very low certainty of the estimates of effect)*

18. *Mycobacterium tuberculosis* antigen-based skin tests (TBST) may be used to test for TB infection. *(Conditional recommendation, very low certainty of the estimates of effect)*

Justification and evidence

Recommendation 17 was originally published in the 2018 WHO guidelines *(17)*. A previous systematic review was updated to compare the predictive performance of IGRA and TST for identifying incident TB disease in countries with a TB incidence > 100/100 00 population *(67)*. Only studies in which TST was compared with IGRA in the same population were considered, and relative risk ratios for TB for people who tested positive and those who tested negative in those two tests were estimated. (See the GRADE evidence summaries for PICO 4 in Annex 3).

Five prospective cohort studies were identified, with a total of 7769 participants; four were newly identified. Three of the studies were conducted in South Africa and two in India *(23,68,69,70,71)*. The studies included people with HIV, pregnant women, adolescents, health-care workers and household contacts. The pooled risk ratio estimate for TST was 1.49 (95% CI, 0.79 ; 2.80) and that for IGRA was 2.03 (95% CI, 1.18 ; 3.50). Although the estimate for IGRA was slightly higher than that for TST, the 95% CIs for the estimates for TST and IGRA overlapped and were imprecise. Furthermore, there was limited evidence for the predictive value of the tests in specific at-risk populations.

The GDG concluded that comparison of TST and IGRA in the same population does not provide strong evidence that one of the tests should be preferred over the other for predicting progression to TB disease. TST may require significantly fewer resources than IGRA and may be more familiar to practitioners in resource-constrained settings; however, recurrent global shortages and stock-outs of TST limit prospects for its scale-up in PMTPT.

The GDG also noted that equity and access could affect the choice and type of test used. The preferences of people to be tested and programmes depend on several factors, such as the requirement for an adequately equipped laboratory (e.g. for IGRA), possible additional costs for people being tested (e.g. for travel) and the programme (e.g. for infrastructure and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages.

The GDG cautioned that imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as people with HIV with low CD4 counts. The GDG noted the importance of the tests for identifying recent conversion from negative to positive, particularly among contacts of people with pulmonary TB, which is good practice when initiating TPT. Nevertheless, studies among health-care workers tested serially for TBI in the USA showed that conversion from negative to positive and reversion from positive to negative are more commonly identified with IGRA than with TST *(72)*. Thus, clinical judgement must still be used to interpret the results of serial TBI tests.

Although some studies suggest otherwise *(73,23)*, the GDG maintained the past position that people with HIV who have a positive test for TBI benefit more from TPT than those who have a negative TBI test *(17,26)*. TBI testing can be used, where feasible, to identify such individuals. The GDG, however, based on evidence of moderate certainty, strongly emphasized that TBI testing by TST or IGRA should not be a prerequisite for starting TPT in people with HIV and in household contacts aged < 5 years, particularly in settings with a high TB incidence (e.g. > 100 TB cases/100 000 population), given that the benefits clearly outweigh the risks. A negative TBI test in these two groups or in HIV-negative infant household contacts should be followed by a case-by-case assessment for the potential benefit and harm of TPT.

In 2022, WHO issued **recommendation 18** on use of new *M. tuberculosis* antigen-based skin tests (TBSTs) to test for TBI *(14)*. A systematic review of published and unpublished data was conducted for new TBSTs based on specific antigens (ESAT-6 and CFP-10), which combine the advantage of a simpler skin test with the specificity of IGRAs. In all tests, antigen is injected intradermally, and, as in the TST, the tests are read after 48–72 h as induration in millimetres, by the method suggested by Mantoux. In 2022, the WHO GDG concluded that the available evidence showed that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST *(14)*. TBSTs are recommended for all subpopulations, including people with HIV, children and adolescents and people who have been vaccinated with the bacille Calmette-Guérin (BCG) vaccine.

Implementation considerations

TBI testing is desirable whenever feasible to identify people at highest risk for developing TB disease. It is not required for people with HIV or in household contacts aged < 5 years. In HIV-negative household contacts aged ≥ 5 years and in other risk groups TBI tests are recommended, but their lack of availability should not be a barrier to providing TPT.

The GDG noted that availability and affordability could determine which TBI test is used. Other considerations include the structure of the health system, the feasibility of implementation and infrastructure requirements.

The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. BCG vaccination decisively reduces the specificity of TST. The GDG noted, however, that the effect of BCG vaccination on the specificity of TST depends on the strain of vaccine used, the age at which the vaccine is given and the number of doses administered. When BCG is given at birth, as recommended by WHO and in practice in most parts of the world, it has a variable, limited impact on TST specificity *(74)*. Therefore, the GDG agreed that a history of BCG vaccination has a limited effect on interpretation of TST results later in life. Hence, BCG vaccination should not be a determining factor in selecting a test.

IGRA testing is more costly than TST and requires appropriate laboratory services. Operational difficulties should be considered in deciding which test to use. For example, IGRA requires a phlebotomy, which can be difficult, particularly in young children; it requires laboratory infrastructure, technical expertise and expensive equipment; and its sensitivity is reduced in children aged < 2 years and those with HIV. Nevertheless, only a single visit is required to conduct an IGRA test (although patients may have to make a second visit to receive the result). Skin testing with TST or TBST is less costly and can be performed in the field, but it requires a cold chain, two health-care visits and training in intradermal injection, reading and interpretation. One other practical advantage of IGRAs over TST is that they are not susceptible to a "booster response", which necessitates a two-step testing approach when the reactivity to TST has waned since infection.

In 2011, WHO recommended use of three IGRA products for testing for TBI: QIAGEN QuantiFERON-Gold, QIAGEN QuantiFERON-TB Gold In-Tube and Oxford Immunotec T-SPOT.TB assays *(75)*. In 2021, the list of WHO-recommended IGRAs was extended to include Beijing Wantai's TB-IGRA and QIAGEN QuantiFERON-TB Gold Plus *(76)*.

The three specific TBST products available for review by the GDG that developed the 2022 WHO recommendations were Cy-Tb (Serum Institute of India, India), Diaskintest® (Generium, Russian Federation) and C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China). Users of the tests might have to issue appropriate guidance and explain the difference between the TST and TBSTs *(64)*. It is also important to standardize measurement of the TBST reaction size and its interpretation. As for TSTs, use of TBSTs requires a cold chain, well-trained, skilled staff to administer and interpret test results and multiuse vials for effective operational planning and batching. Procurement and stock management should be considered, including availability on the global market, as for any new class of tests. TBSTs might require regulatory approval from national authorities or other relevant bodies, as they are a relatively new in-vivo tests.

TST, TBST and IGRA are not validated for confirmation of TB disease and should therefore not be used to diagnose TB nor for the diagnostic workup of adults being evaluated for TB disease.

1.4 TB preventive treatment options

TPTs for an infection with *M. tuberculosis* strains presumed to be drug-susceptible can be broadly categorized into two types: monotherapy with isoniazid for at least 6 months (IPT) and treatment with regimens containing a rifamycin (rifampicin or rifapentine). IPT has been the most widely used form of TPT, but the shorter duration of rifamycin regimens presents a clear advantage, making these regimens increasingly preferred. TPT for MDR/RR-TB requires a different approach, primarily with levofloxacin. The recommendations for these treatment options and the conditions under which they apply are discussed below.

19. The following TB preventive treatment options are recommended regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate-to-high certainty of the estimates of effect)*.

20. The following alternative TB preventive treatment options may be used regardless of HIV status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin. *(Conditional recommendation, low to moderate certainty of the estimates of effect)*.

TPT with isoniazid or rifamycins

A strong recommendation for TPT alternatives to 6 months of daily isoniazid monotherapy (6H), based on evidence of moderate to high certainty, has featured in previous WHO guidance *(17,37,77)*. These consist of 3 months of weekly isoniazid plus rifapentine (3HP) and 3 months of daily isoniazid plus rifampicin (3HR). In the 2020 guidelines, the GDG made conditional recommendations for two regimens: daily rifapentine plus isoniazid for 1 month (1HP) and daily rifampicin monotherapy for 4 months (4R) in all settings, based on low to moderate certainty of the estimates of effect. In the current second edition, the recommendation from 2020 has been divided: **recommendation 19** for regimens that are strongly recommended and **recommendation 20** for alternative regimen options. Recommended TPT options are applicable in all settings, regardless of TB burden.

Justification and evidence

Daily isoniazid monotherapy

The efficacy of 6H or more has been shown in different populations and settings in a number of systematic reviews *(21,78,79)*. A systematic review of RCTs in people with HIV showed that isoniazid

monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51 ; 0.87) and that preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22 ; 0.61) *(21)*. Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months of daily isoniazid monotherapy (RR 0.58; 95% CI 0.3 ; 1.12). A systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (odds ratio [OR] 0.65; 95% CI 0.50 ; 0.83) *(80)*. No controlled clinical trials were found of daily isoniazid monotherapy for 9 months (9H) versus 6H. Re-analysis and modelling of the US Public Health Service trials of isoniazid conducted in the 1950s and 1960s, however, showed that the benefit of isoniazid increases progressively when it is given for up to 9–10 months and stabilizes thereafter *(81)*. For this reason, 9H is retained as an alternative regimen to 6H in the recommended TPT options.

Until the 2020 updated guidelines, daily IPT for 36 months was conditionally recommended for adults and adolescents with HIV, regardless of whether they were receiving ART, in settings with a high risk of TB transmission *(82)*. This recommendation was based on low-certainty evidence from a systematic review and meta-analysis of three RCTs *(78)*. In two of the studies reviewed, ART was not used, and, in the third, ART coverage was low at baseline but increased during the period of observation. The GDG for this second edition of the TPT guidelines decided to withdraw this recommendation given its poor uptake by countries since its release in 2011. In the past decade, access to ART has increased substantially worldwide, and shorter TPT options are preferred to isoniazid monotherapy.

Weekly rifapentine plus isoniazid for 3 months (3HP)

A systematic review was conducted for the 2018 update of the guidelines to compare the effectiveness of 3HP with that of isoniazid monotherapy. The review was of four RCTs *(84–87)*, which were analysed for three subgroups: adults with HIV infection, adults without HIV infection and children and adolescents (2–17 years) who could not be stratified according to HIV status because the relevant studies were lacking. The evidence base for this revised recommendation is summarized in the GRADE tables for PICO 8 in annexes 3 and 4.

Two of the RCTs involved adults with HIV in Peru, South Africa and a number of countries with a TB incidence < 100/100 000 population. No significant difference in the incidence of TB disease was found between participants given 3HP and 6H or 9H (RR 0.73, 95% CI 0.23 ; 2.30). Furthermore, the risk for hepatotoxicity was significantly lower with 3HP in both adults with HIV (RR 0.26, 95% CI 0.12 ; 0.55) and those without HIV (RR 0.16, 95% CI 0.10 ; 0.27). The 3HP regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01 ; 1.55; adults without HIV: RR 1.19, 95% CI 1.16 ; 1.22; children and adolescents: RR 1.09, 95% CI 1.03 ; 1.15). One RCT included a comparison between 3HP and continuous isoniazid monotherapy in adults with HIV *(84)*. No significant difference in TB incidence was found in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TBI or death among participants given continuous isoniazid. In all the studies, 3HP was given under direct observation.

Daily rifampicin plus isoniazid for 3 months (3HR)

A systematic review updated in 2017 showed that the efficacy and the safety profile of 3–4 months of daily rifampicin plus isoniazid were similar to those of 6 months of isoniazid *(80,88)*. A previous GDG therefore strongly recommended that daily rifampicin plus isoniazid be used as an alternative to isoniazid in settings with a TB incidence < 100/100 000 population *(37)*. A review of studies in which the effectiveness of rifampicin plus isoniazid daily for 3 months was compared with that of isoniazid for 6 or 9 months in children comprised one RCT and two observational studies *(89–91)*. (See also GRADE evidence summaries for PICO 5 in annexes 3 and 4.) The RCT found no clinical disease in either group when new radiographic findings suggestive of TB disease were used as a proxy for clinical disease *(90)*. Fewer participants given daily rifampicin plus isoniazid than those given 9 months of isoniazid developed radiographic changes (RR 0.49, 95% CI 0.32 ; 0.76). The authors also reported a

lower risk for adverse events (RR 0.33, 95% CI 0.20 ; 0.56) and a higher adherence rate (RR 1.07, 95% CI 1.01 ; 1.14) among children given daily rifampicin plus isoniazid. Similar findings were reported in the observational studies *(89,91)*.

Daily rifapentine plus isoniazid for 1 month (1HP)

Before updating the 2020 guidelines, the GDG considered data from the only known published study of the 1HP regimen: a randomized, open-label, phase 3 non-inferiority trial of the efficacy and safety of 1HP as compared with 9 months of isoniazid alone (9H) in people with HIV aged ≥ 13 years in areas of high TB prevalence or who had evidence of TBI *(92)*. Enrolment was restricted to individuals who were not pregnant or breastfeeding. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was < 1.25. For all study participants, the difference in the incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% CI −0.35 ; +0.30); the RR for treatment completion of 1HP as compared with 9H was 1.04 (95% CI, 0.99 ; 1.10); the RR for grade 3–5 adverse events was 0.86 (95% CI, 0.58 ; 1.27); the hazard ratio for death from any cause was 0.75 in favour of 1HP (95% CI, 0.42 ; 1.31); and the RRs for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17 ; 15.99) and 0.81 (95% CI, 0.06 ; 11.77). Overall non-inferiority as defined by the study protocol was shown in the modified intention-to-treat population. Non-inferiority was also shown for the sub-group with confirmed TBI (incidence rate difference per 100 person-years = 0.069 [–0.830 to 0.690]) in males and females and among people on or not on ART at the start of the study. Few patients had a CD4+ < 250 cells/mm^3, and neither inferiority or noninferiority of 1HP was shown in this stratum. The evidence for this recommendation is summarized in the GRADE tables for PICO 7 in annexes 3 and 4.

Daily rifampicin monotherapy for 4 months (4R)

A systematic review conducted for the 2015 TPT guidelines and updated in 2017 found similar efficacy for 3–4 months' daily rifampicin and 6H (odds ratio, 0.78; 95% CI, 0.41 ; 1.46) *(80,88)*. The review also showed that individuals given rifampicin daily for 3–4 months had a lower risk for hepatotoxicity than those treated with isoniazid monotherapy (OR 0.03; 95% CI 0.00 ; 0.48).

Before the 2020 guidelines were updated, the GDG discussed the implications of using 4R in high TB burden settings based on findings from RCTs of 4R vs 9H that included adults and children in such countries *(93–96)*. In study participants aged > 17 years, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was < 0.01 cases per 100 person-years (95% CI, −0.14 ; 0.16); the difference in treatment completion was 15.1% (95% CI, 12.7 ; 17.4); and the difference in grade 3–5 adverse events was −1.1% (95% CI −1.9 ; –0.4). In individuals < 18 years, the difference in the rate of TB disease between 4R and 9H was –0.37 cases per 100 person-years (95% CI, −0.88 ; 0.14); the difference in treatment completion was 13.4% (95% CI, 7.5 ; 19.3); and the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was −0.0 (95% CI, −0.1 ; 0.1). The evidence for this revised recommendation is summarized in the GRADE tables for PICO 6 in annexes 3 and 4.

Implementation and subgroup considerations

The GDG agreed that the benefits of all the treatment options being recommended outweigh their potential harm. Programmes and clinicians should also consider the characteristics of each individual concerned to maximize the likelihood that treatment is completed as expected. The decision on which treatment to offer should not be confined to the manner in which it was studied in a trial (e.g. 1HP to replace 9H) but by considerations such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability – including child-friendly formulations – and the individual's preferences. All recommended treatment options are possible in people with HIV.

On the basis of existing practice, albeit in the absence of a direct comparison, the GDG judged that 9H is an equivalent option to 6H in countries with a strong health infrastructure. It noted, however, that 6H is preferable to 9H from the point of view of feasibility, resource requirements and acceptability to people who need TPT. Nonetheless, both 6H and 9H have become less preferable for TPT as shorter rifamycin-containing regimens become more widely available, as they facilitate administration for both the person taking them and health-care services. The conditional recommendation to give at least 36 months of daily isoniazid monotherapy to people with HIV in high TB transmission settings is now considered obsolete and has been withdrawn in this second edition of the consolidated guidelines on TPT (see above).

The GDG agreed unanimously that, in individuals aged < 15 years, the benefits of 3HR outweigh the harm, given the safety profile of this regimen, the higher rate of completion as compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid. The GDG therefore made a strong recommendation despite the low certainty of the evidence. Data on the safety and pharmacology of rifapentine in children < 2 years have recently become available, which make it possible to administer the 3HP regimen even to children in this age group *(12,98)*. The data from the 1HP trial reviewed for the 2020 update of the guidelines relate only to individuals with HIV aged ≥ 13 years. The GDG considered that extrapolation of the effects to children aged 2–12 years is reasonable, although the daily dosage of rifapentine in this age group has yet to be established. In the absence of further data, the 1HP regimen thus continues to be recommended only for individuals aged ≥ 13 years.

The GDG that prepared the 2020 update of the guidelines considered that there was moderate certainty that 4R is not inferior to 9H. When considering the good safety profile of the 4R regimen and its reduced length, it also recommended that this regimen could also be used in high TB-burden settings. When deciding to make a conditional recommendation, the GDG considered that most people would prefer a shorter regimen but raised concern about the variable acceptability; uncertainty in resource requirements, given its higher cost; the feasibility of delivering appropriate dosages in lower weight bands with the current formulation of single-dose rifampicin capsules; and a potential reduction in equity if it deflects resources and decreases the treatment coverage of more vulnerable individuals. The GDG agreed that introduction of 4R should be preceded by mobilization of appropriate resources to avoid shortages in other programmatic needs. The GDG also observed that the impact on equity could change if the price and policy of use of 4R changed. (See Annex 4 for more details of the GDG decisions.)

With respect to 1HP, the GDG that prepared the 2020 update of the guidelines concluded that there was low certainty that its effectiveness would be non-inferior to 9H when used in programmatic settings for different populations at risk. When also taking into account the good safety profile of 1HP and the much shorter regimen than other approved TBI regimens, the GDG recommended that this regimen could also be used in high TB-burden settings and in people without HIV infection. The GDG considered that most people would prefer its much shorter duration over other options and that its implementation would be feasible but raised concern about uncertain resource requirements and potentially reduced equity. These considerations led to a conditional recommendation. (See Annex 4 for more details of the GDG decisions).

In the update to the 2020 guidelines, the GDG considered that all regimens could be used in any setting, regardless of TB burden, provided that the health infrastructure could ensure that treatment is given correctly without creating inequity and that TB disease could be excluded reliably before initiation of treatment.

The GDG noted that all the TPT regimens can be self-administered. A number of recent trials and other studies attest to the feasibility of self-administered treatment of 3HP as compared with directly observed treatment *(28,99–101)*. The GDG noted that a requirement for direct observation could be a significant barrier to implementation. People receiving TPT should be supported with advice on treatment and management of adverse events during encounters with health services. The GDG

further noted that individuals receiving treatment, clinicians providing treatment and programme managers would prefer shorter to longer regimens.

Drug–drug interactions

Rifamycins induce certain cytochrome P-450 enzymes and may therefore interfere with medicines that depend on this metabolic pathway by accelerating their elimination. These medicines include ART and many other medicines, such as anticonvulsants, antiarrhythmics, quinine, oral anticoagulants, antifungals, oral and injectable contraceptives, corticosteroids, cyclosporine, fluoroquinolones and other antimicrobials, oral hypoglycaemic agents, methadone and tricyclic antidepressants. These medicines might therefore have to be avoided when taking rifampicin- or rifapentine-containing regimens or their dosages should be adjusted.

TPT regimens containing rifampicin or rifapentine should be prescribed with caution to people with HIV who are on certain ART because of potential drug–drug interactions. TPT regimens can significantly decrease the concentrations of boosted protease inhibitors or nevirapine and should not be co-administered, including to HIV-exposed infants on TPT.

The results of a phase 1/2 clinical trial of 3HP and dolutegravir in adults with HIV indicate good tolerance and viral load suppression, no adverse events higher than grade 3 related to 3HP, and do not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment *(102)*. Recent work continues to support this position *(103–105)*. Preliminary evidence from the phase 1/2 trial also supports an immediate start of TPT among ART-naive people starting a dolutegravir-based regimen. When 3HP was administered to 50 people with HIV who were ART-naive and who were started on dolutegravir-containing ART, high rates of viral suppression, comparable to those with 6H, were achieved, and no difference in grade 3 or 4 adverse events was observed *(105)*. Administration of rifapentine with raltegravir was also found to be safe and well tolerated *(106)*. The 3HP regimen can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics *(107)*.

No dose adjustment is required when rifampicin is co-administered with efavirenz, and the two drugs can be used together safely. When given with rifampicin, however, the dose of dolutegravir has to be increased to 50 mg twice daily *(108)*, a dose that is usually well tolerated and shows equivalent efficacy as efavirenz in viral suppression and recovery of CD4 cell count.

Concurrent use of alcohol should be avoided with all TPT regimens.

Pregnancy

In preparation for the 2020 update of the guidelines, a systematic review was conducted in 2019 to assess evidence in support of or against the results of one RCT that showed adverse pregnancy outcomes associated with use of IPT *(109,110)*. Further, three non-randomized, comparative observational studies provided data on at least one of the pregnancy outcomes in women with HIV *(111–113)* (see PICO 9 in Annex 3). While the RCT showed a higher risk of adverse pregnancy outcomes in women who initiated IPT during pregnancy (Mantel-Haenszel OR stratified by gestational age, 1.51 95% CI 1.09 ; 2.10), all three of the other studies reported an overall OR < 1, suggesting the opposite (I^2=80%, *P*=0.002). A meta-analysis of two observational studies that reported adjusted estimates and the data of which could be pooled suggested a lower risk for composite adverse pregnancy outcomes (OR 0.40, 95% CI 0.20 ; 0.74) *(111,112)*. The observational studies did not reproduce the associations with IPT reported in the RCT for individual adverse outcomes, such as fetal or neonatal death, prematurity, low birth weight and congenital anomaly. No statistically significant risks for maternal hepatotoxicity, grade 3 or 4 events or death were reported in any of the four studies. The GDG therefore concluded that there were insufficient grounds to change previous guidance or to develop a separate recommendation for use of IPT in pregnant women with HIV, and no evidence-to-decision table was developed for this PICO in Annex 4. The GDG considered that systematic deferral

of IPT to the post-partum period would deprive women of its protective effect at a time when they are more vulnerable to TB. Moreover, a study published in 2023 showed no difference in acquisition of TB in the infants of mothers with HIV who received IPT during pregnancy and those who received it post partum *(114)*. Appropriate care during the antenatal and postnatal periods and during delivery may reduce the risk of adverse pregnancy outcomes. While baseline testing for liver function is strongly encouraged when IPT is given during pregnancy, it is not required, and routine liver function testing when IPT is given in pregnancy is not indicated unless other risk factors for liver toxicity are present. Routine vitamin B6 supplementation should nevertheless be considered. The GDG agreed that the area requires more research, such as on the pharmacokinetics of IPT, pharmacovigilance and other preventive treatment regimens. Rifampicin is generally considered safe in pregnancy. There are few data on the pharmacokinetics and safety of rifapentine in pregnancy, precluding use of 3HP and 1HP in pregnancy until more information on the appropriate dosing and safety of these regimens becomes available. In a study of 3HP in 112 pregnant women, the rates of spontaneous abortion and birth defects were similar to those in the general US population *(97)*. Moreover, the results of a recent trial in Africa showed that the frequency of spontaneous abortion and adverse pregnancy outcomes (when analysed as a composite outcome) were similar in 63 women exposed to 3HP and in 142 women who were not exposed to 3HP *(115)*.

Other subgroups and settings

In candidates for transplantation or anti-TNF treatment, it may be particularly important to complete TPT rapidly; therefore, shorter regimens such as 1HP and 3HP could be advantageous. Likewise, shorter treatment could be more suitable than longer regimens for homeless people and people being released from prison, for whom there is limited opportunity for repeated encounters for treatment.

Other populations, in addition to people with HIV on ART, who may be more commonly at risk of drug–drug interactions with rifampicin, include women of childbearing age on contraceptive medicines (who should be counselled about potential interactions and consider nonhormonal birth control while receiving rifampicin) and opiate users on substitution therapy with methadone.

Other considerations

With the widespread use of rifampicin-containing fixed-dose combinations to treat drug-susceptible TB, the demand by TB programmes for single-dose rifampicin has decreased. Quality-assured supplies of rifampicin should be used. Provision of 4R outside TB programme centres (e.g. primary care facilities, HIV programmes) should be accompanied by stepwise guidance on maximizing the effect of rifampicin and on avoiding its diversion for improper use as a broad-spectrum antibiotic in the community.

Fixed-dose combinations of rifampicin plus isoniazid – including dispersible formulations for children – should be used when possible to reduce the number of pills to be taken. Combinations of 300 mg isoniazid with 300 mg rifapentine are now also available, which will facilitate administration of 3HP to adults *(12)*. For children, dispersible formulations of both isoniazid and rifapentine can facilitate administration of 3HP. Shorter regimens are also more likely to be completed. Concern about adherence should not be a barrier to starting TPT, and support should be provided to ensure better person-centred care. There are no data-supported recommendations on handling interruptions of TPT, such as on how many missed doses can be made up for by prolonging treatment without compromising efficacy.

Individuals at risk of peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes or who are pregnant or breastfeeding, should receive pyridoxine (vitamin B6) when taking isoniazid-containing regimens. A different dose of isoniazid from that proposed might be required to avoid toxicity if there is a high population prevalence of "slow acetylators". Combination tablets of co-trimoxazole, isoniazid and pyridoxine could be given to people with HIV. Lack of availability of pyridoxine should not be a reason for withholding TPT.

Interventions to enhance adherence and completion of treatment should be tailored to each risk group and local context. A systematic review conducted for the WHO 2015 TPT guidelines provided heterogeneous results for interventions to improve treatment adherence and completion, and the evidence was considered inconclusive *(39)*. WHO guidance for TB care and support includes several interventions to support adherence, which could also be applied to TPT *(116,117)*.

In areas with high background resistance to rifampicin, such as countries in eastern Europe, it is particularly important to test the strain from the presumed source for drug susceptibility so that TPT is more likely to work. Contacts of patients with laboratory-confirmed isoniazid-resistant, rifampicin-susceptible TB may be offered a 4-month regimen of daily rifampicin. If there is rifampicin monoresistance or other contraindications to rifampicin, an isoniazid regimen of ≥ 6 months may be the most appropriate option. Unfortunately, in many settings, rifampicin resistance is often accompanied by isoniazid resistance – MDR-TB – so that other drugs are required (see below).

TB preventive treatment with levofloxacin

21. In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, 6 months of daily levofloxacin should be used as TB preventive treatment. *(Strong recommendation, moderate certainty of the estimates of effect)*.

Drug-resistant TB is one of the most prominent causes of morbidity and mortality from an antimicrobial-resistant organism. It is thus important to take all measures possible to lower the risk of secondary cases of MDR/RR-TB. This includes use of appropriate TPT with regimens of proven effectiveness. Recommendation 21 was first issued in this edition of the consolidated guidelines and is based on moderately certain evidence, as summarized in the GRADE tables (see PICO 10 in annexes 3 and 4). The current recommendation replaces the previous conditional recommendation for TPT in selected household contacts of MDR/RR-TB that was issued in 2018 that was based on very low certainty of the estimates of effect *(39)*.

Justification and evidence

Before this second edition of the guidelines, the GDG considered evidence from two randomized controlled trials, TB CHAMP and V-QUIN *(15,16)*, and a systematic review commissioned by WHO on TPT for MDR/RR-TB (Annex 5). In addition, studies on the programmatic feasibility and acceptability of 6Lfx were conducted. In contrast, the previous WHO recommendation in the 2018 guidelines was based on a review of 10 studies, none of which was an RCT. Overall, 6Lfx reduced the risk of TB by 62% over 1 year among household contacts of people with MDR/RR-TB (RR 0.38; 95% CI 0.17 ; 0.86), with similar effects in the two trials: hazard ratio, 0.44; 95% CI 0.15 ; 1.25 for TB CHAMP and 0.34; 95% CI 0.09 ; 1.25 for V-QUIN. A Bayesian analysis of data from the two clinical trials gave similar findings, with credible intervals showing a statistically significant difference from 1 (hazard ratio, 0.38; 95% credible interval, 0.15 ; 0.94 in TB CHAMP and 0.41; 95% credible interval, 0.18 ; 0.95 in V-QUIN).

A systematic review of relevant studies published between June 2016 and September 2023 comprised three observational studies of TB prevention with fluoroquinolones (alone or in combination with other TB drugs), and one assessed prevention of TB with isoniazid. All four were observational studies with substantial risk of bias, notably selection bias. Data from these studies could not be pooled for a joint analysis. An analysis of unpublished data on 496 527 individual contacts identified 8952 contacts of patients with MDR/RR-TB of whom 722 received isoniazid and 4223 received no TPT. The reasons for initiating or not initiating isoniazid and the duration of isoniazid were not given, and data on completion of TPT, concomitant exposure and drug sensitivity patterns in the untreated group that developed disease were not available. The GDG noted that the findings on effectiveness, survival and completion were inconclusive and considered that the analysis – and also a published study of IPT in

contacts of cases of MDR-TB *(118)* – did not fully address the PICO question (effects of levofloxacin vs other or no TPT). (For more details, see annexes 3 and 4.)

The treatment completion rate in the levofloxacin arm was 86% in TB CHAMP (placebo arm: 86%) and 70% in V-QUIN (placebo arm: 85%), with RRs of 1.00 [95% CI 0.95 ; 1.06] and 0.83 [0.79 ; 0.87], respectively. There was an important difference in the risk of adverse events between children and adults, with very good tolerance in children, which decreased with age. This probably contributed to poorer adherence to TPT by the participants in the V-QUIN. The prevalence of adverse events of grade 3 or more was not significantly higher in the TB CHAMP trial among people < 18 years receiving 6Lfx (RR 0.53, 95% CI 0.16 ; 1.70), but significantly higher rates were found in the V-QUIN trial, in which 97% of participants were > 14 years (RR 5.26, 95% CI 1.16 ; 23.95). Overall, the likelihood of treatment discontinuation among individuals on 6LFx with adverse events of any grade was high (RR 6.32, 95% CI 3.43 ; 11.63), occurring in 43 more patients out of 1000 (range, 20–89). Microbiological studies within both trials did not provide conclusive evidence of the emergence of additional fluoroquinolone resistance in TB strains or in microbiota other than *M. tuberculosis* (e.g. gut flora) at the time of analysis.

A systematic review of studies published between June 2016 and September 2023 identified five observational studies of adverse events with fluoroquinolone (alone or in combination with other TB drugs). All were observational studies with substantial risk of bias, notably selection and ascertainment bias. Fluoroquinolone monotherapy with levofloxacin, ofloxacin or moxifloxacin was found to be generally safe in three studies, with some mild or moderate drug-related adverse events in children but no grade 3 or 4 or serious adverse events reported. (For more details, see annexes 4 and 5.) No evidence was found to support shortening of levofloxacin TPT to < 6 months or its prolongation beyond 6 months.

Subgroup considerations

Children and adolescents: Levofloxacin can be used in children and adolescents, in whom completion and tolerability in the TB CHAMP trial (which included only individuals aged < 18 years) were much better than in the V-QUIN trial (in which 97% of participants were aged ≥ 15 years). There is no requirement to test for TBI before starting levofloxacin in children who are contacts of people with MDR/RR-TB. Although there has been concern about use of fluoroquinolones in children because of retardation of cartilage development shown in juvenile animals exposed to these agents *(119)*, similar effects have not been found in humans *(120,121)*.

Pregnancy and breastfeeding: TPT with levofloxacin in pregnancy requires a risk–benefit assessment and an informed choice by pregnant woman on whether to take TPT or to defer TPT to the end of pregnancy. The advice should depend on the circumstances (e.g. first trimester versus later). Pregnancy increases the risk of progression from infection to disease and the risk of poor maternal and fetal outcomes should TB disease occur. MDR/RR-TB in pregnancy is a serious condition, and some of the drugs used to treat MDR-TB may be toxic to the fetus. Observations from studies in animals exposed to levofloxacin have limited its use in pregnancy; however, one meta-analysis of observational studies with 2800 pregnant women given fluoroquinolones for any indication (e.g. urinary tract infection) found no difference in the incidence of birth defects, spontaneous abortion or prematurity from that in unexposed pregnant women *(122)*. The concentrations of levofloxacin in breastmilk appeared to be far lower than the dose for infants and would not be expected to cause adverse effects in breastfed infants *(123)*. Its use should therefore not be suspended during breastfeeding. While effects of fluoroquinolones on bone and cartilage observed in animals have not been seen in humans, the data and follow-up times of infants are limited. Recent alerts have, however, highlighted safety concerns associated with prolonged use of fluoroquinolones in humans *(124–126)*.

HIV infection: Levofloxacin can be used in people with HIV. No specific drug–drug interaction with ART has been observed in people with HIV exposed to MDR/RR-TB, and there is no need to test for infection before starting levofloxacin.

Contraindication: Levofloxacin should not be given to people who are allergic to fluoroquinolone, who have another contraindication to the same class of drugs or when there is potential drug–drug interaction. Levofloxacin should be discontinued if the person develops a serious or severe adverse drug reaction. (See below for other TPT regimen options in such a case.)

Implementation considerations

The strong recommendation reflects the GDG opinion that the benefits of levofloxacin outweigh the potential harm in most people who are eligible to receive it. Health programmes and clinicians should strictly ensure eligibility for its use, maximize the likelihood of treatment completion as expected and ensure that contacts are followed up regardless of whether TPT was completed. Contacts of people with RR-TB are usually treated as for MDR-TB, unless susceptibility to isoniazid is reliably confirmed in the index person, in which case isoniazid may be considered an effective TPT option.

The GDG considered that levofloxacin could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure that treatment is given correctly without creating inequity, and that TB disease can be excluded reliably before initiation of treatment. Levofloxacin is widely available as a generic drug, in both adult and paediatric formulations. As for other TPT, the GDG noted that treatment can be self-administered and that a requirement for direct observation could be a significant barrier to implementation. Digital adherence technologies (e.g. electronic medication monitors) may be used, but few studies have been conducted on their use for TPT. The GDG noted that the 6-month duration of levofloxacin treatment may appear long to patients and caregivers when compared with the shorter, 4- or 12-week TPT regimens that are now available for prevention of drug-susceptible TB. People receiving TPT should also be provided with advice on treatment and management of adverse events.

Levofloxacin is the preferred fluoroquinolone for use in TPT, and it was used in both trials. Instructions on dosage are provided in the WHO operational handbook on TPT *(12)*. While there are no comparable data on alternatives, moxifloxacin can be used if levofloxacin is not available. Drug-susceptibility testing of the source case strain would provide important additional information, especially in situations where fluoroquinolone resistance is known to be high. If the strain in the source patient is resistant to these medicines, other TB drugs (e.g. ethionamide, ethambutol) can be used as TPT according to the best available information on the drug susceptibility profile of the presumed strain. In this case, the certainty of the effectiveness of TPT is much lower than with levofloxacin (see also below). A positive test for TBI before starting TPT for MDR/RR-TB is not required for child contacts or people with immunocompromising conditions. In other populations, this would be desirable but not mandatory. Lack of availability of testing should not be a barrier to providing TPT to individuals who are at risk. Screening of all household and other close contacts for co-prevalent TB disease will be important. The approach to screening and ruling out TB in contacts is otherwise no different from that described earlier (see section 1.2). Provision of TPT with levofloxacin should include consideration of factors such as age, risk of toxicity or interaction, co-morbidity, the susceptibility to drugs of the strain of the most likely source case, background resistance to fluoroquinolones in MDR/RR-TB strains, availability and the individual's preferences.

The capacity of a programme to provide TPT for MDR/RR-TB should be carefully planned to ensure that all the necessary resources are in place, including programme capacity to rule out TB disease, perform quality-assured testing for drug susceptibility in the presumed source case, deliver the necessary medications and closely monitor adverse events and emergence of TB disease. Engagement of stakeholders in the community is important, as for other means to address constraints to implementation.

A paediatric formulation of levofloxacin can be used. Instructions on dosage are provided in the WHO operational handbook on TPT *(12)*. If fluoroquinolones cannot be used because of intolerance or resistance in the strain from the presumed source case, treatment with the other TB drugs used in some studies may be considered (e.g. ethambutol, ethionamide), although the evidence for their

efficacy is much less certain *(127,128)*. While ethambutol is considered safe in pregnancy, ethionamide has been associated with teratogenic potential at high doses in experimental animals, although there are minimal data on human pregnancy. There is limited evidence for the optimal duration of MDR-TB preventive treatment, which should be based on clinical judgement. In the studies conducted so far, levofloxacin was given for 6, 9 or 12 months. None of studies included studies of pharmacokinetics or safety in pregnancy or a comparison of risks for adverse events, although one reported no serious adverse events attributable to fluoroquinolone-based preventive treatment *(104)*.

2. Monitoring and evaluation

Coverage of contact investigation and TPT among child contacts and people with HIV are two of the top 10 core indicators for monitoring implementation of the End TB Strategy *(8)*. National TB and HIV programmes report data yearly to WHO and UNAIDS on progress in PMTPT in target populations *(41,130)*. PMTPT should include monitoring and evaluation systems that are aligned with national TB patient monitoring and surveillance systems. They should include coverage of TPT with levofloxacin among contacts exposed to MDR/RR-TB. Appropriate recording and reporting tools should be available. Electronic case-based monitoring will facilitate PMTPT. Standardized indicators should be measured regularly to inform decision-makers for programme implementation. Some may require changes to national regulations or health policies (e.g. making TBI a notifiable condition or mandating a reporting framework), which should be addressed according to the context. The private health sector should be engaged to ensure proper recording and reporting from both the private and public sectors. More details on monitoring and evaluation are provided in the second edition of the WHO operational handbook on TB preventive treatment *(12)*. Monitoring should adhere with ethical principles of surveillance *(131)*.

Most individuals who receive TPT are healthy, and adverse reactions to treatment are likely to influence the likelihood of their completing it. Drug-related toxicity should therefore be minimized. Medicines used in TPT regimens are generally safe and well tolerated, but adverse reactions have been observed with isoniazid (particularly asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity), rifampicin and rifapentine (such as cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity) and levofloxacin (such as arthritis, arthralgia, or tendinopathy) *(124–126)*. While most of these reactions are minor and occur rarely, attention should be paid to preventing conditions such as drug-induced hepatotoxicity. Caregivers should be aware of the spectrum of adverse reactions associated with use of the drugs so that they can take action rapidly. Most reactions are minor and self-limiting, and severe or serious reactions occur less commonly.

Close monitoring for adverse events and of adherence to treatment is essential for people on TPT for MDR/RR-TB. The GDG reiterated that strict clinical observation and close monitoring for TB disease, based on sound clinical practice and national guidelines, is required for at least 1 year after exposure to MDR/RR-TB, regardless of whether TPT was given. Consideration should also be given to interactions with other medicines when providing TPT for MDR/RR-TB.

Individuals on TPT should be monitored routinely at monthly encounters with health-care providers, who should explain risk, how TB disease develops and the rationale for the treatment and emphasize the importance of completing it. They should also be advised to contact their health-care provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, inflamed or torn tendons, muscle pain, difficulty in walking, paraesthesia, burning pain, dark-coloured urine, pale stools, jaundice, confusion or drowsiness, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell. If a health-care provider cannot be consulted at the onset of such symptoms, treatment should be stopped immediately. This is a critical area in which front-line health-care workers and students should receive training.

There is insufficient evidence to support systematic testing of baseline liver function in people on regimens containing isoniazid and/or rifamycins *(132)*. This is, however, strongly encouraged, where

feasible and resources permit, for individuals with the following risk factors: history of liver disease, harmful use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate post-partum period (within 3 months of delivery). For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TPT outweighs the risks, with routine testing at subsequent visits. Appropriate laboratory testing should also be performed for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Trial criteria for stopping a medicine, such as an increase in transaminases to five times the upper limit of normal or to three times plus symptoms in people on rifampicin, should be adapted to more practical terms for field conditions. (See further instructions in the WHO operational handbook on TPT *(12)*).

There is no evidence that use of isoniazid, rifamycins or levofloxacin for TPT contributes significantly to the emergence of additional drug resistance to TB medicines *(133,134)*. Nonetheless, TB disease must be excluded before TPT is initiated (section 1.2), and regular follow-up is necessary to ensure early identification of people who develop TB disease while receiving TPT. National surveillance systems for anti-TB drug resistance might have to be strengthened in countries in which PMTPT is being scaled up.

Monitoring adherence to TPT and ensuring its completion are of clinical benefit. Electronic applications for mobile phones and other devices can be used to guide national programmes on the critical data to be collected during TB preventive care, in addition to monitoring and evaluation *(135)*. Such applications could also be helpful for collecting information about the occurrence of TB disease in people who have received TPT, by asking patients registered for TB treatment about any history of starting or completing TPT or by cross-linking registers (e.g. registers of people given TPT with TB treatment or mortality registers). In people who develop TB after or well into TPT, emergence of resistance should be tested.

3. Research gaps

The review of evidence for the current update exposed additional knowledge gaps to those reported in other recent updates of the guidelines. Continued research on development and on implementation remains critical for many aspects of PMTPT *(136)*. Some information can be collected from user feedback.

Risks for progression to TB disease

Evidence of the likelihood of progression from infection to TB disease, including MDR/RR-TB, in different populations at risk will help in determining the potential benefits of TPT and in designing appropriate public health interventions. In particular, strong evidence from individually randomized controlled clinical trials is lacking, particularly for indigenous populations and people with the following: diabetes, harmful use of alcohol, tobacco smoking, underweight, fibrotic lesions in the lung on CXR, on steroid treatment, with rheumatological diseases, chronic kidney disease, cancer or COVID-19. Methods for measuring TB incidence directly and also the risk for TB disease could be explored, such as use of genotyping to distinguish between reactivation and reinfection. Evidence is also required on differential harm and the acceptability of testing and treating TBI in specific risk groups, including socially adverse effects such as stigmatization.

Defining the best algorithm for screening and ruling out TB disease

Operational and clinical studies should be conducted to exclude TB disease before TPT is given. The performance and feasibility of the algorithms proposed in these guidelines should be assessed. Data on children and pregnant women in particular are limited. Better evidence is necessary to identify the best strategies for tracing contacts, saving costs and improving feasibility (e.g. use of mobile CXR, including CAD, in people < 15 years).

For all populations and tools, more research is required to evaluate the accuracy and effectiveness of complete screening and diagnostic algorithms, including symptom screening, CXR, CRP, mWRDs and other tools used in various combinations with diagnostic evaluation to rule out TB. Research on their effectiveness should include measures of the impact on patient-important outcomes, such as mortality and treatment success. For people with HIV in settings with different TB burdens, more research is necessary to evaluate the accuracy and predictive value of measuring CRP above any cut-off higher than 5 mg/L for TB screening, when it is used either alone or in combination with other screening tests. More data are also necessary on the effectiveness, cost–effectiveness, feasibility and acceptability, frequency and optimal periodicity of routine, regular screening with the W4SS, CRP, CXR and mWRD among people with HIV. More research is also required on the potential value of screening people with HIV with mWRDs on specimens other than sputum.

Improved diagnostic tests and performance of tests of TBI in populations at risk

Diagnostic tests with better performance and predictive value for progression to TB disease are critical. In addition, the performance of tests of TBI should be evaluated in various risk groups, to assess reinfection and to understand how best to use available tools in each population (e.g. combination or sequential use of skin tests and IGRA). Targeted research to identify more accurate IGRAs is strongly encouraged.

While TBSTs are now recommended for TBI, there are gaps in the evidence, such as the specificity of the Diaskin test and C-TST in populations with a low prevalence of TBI by direct head-to-head comparisons of all three TBSTs; barriers to implementation and patient access; additional studies of accuracy in high-risk groups such as children and adolescents, people with HIV, prisoners and migrants; the epidemiological and economic impact of TBST use in the TBI diagnosis and TPT cascade; the predictive value for TB disease as compared with current tests; the cost and cost–effectiveness of TBSTs in various scenarios; and studies of the use of digital tools for reading results in order to avoid return visits.

TPT options

Research to find shorter, better-tolerated TPT regimens than those currently recommended remains a priority. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people who engage in harmful use of alcohol and older people) are essential. There are very few data on the use of rifapentine in pregnant women. Data on use of 1HP in children and adults not infected with HIV and in people with HIV with low CD4 counts, in various settings, would also be desirable. A direct comparison of 1HP and 3HP for safety, effectiveness and cost-effectiveness would be useful, and the results of ongoing studies are expected in the near future *(137,138)*. Pharmacokinetics studies could help to establish an optimal daily dosage of rifapentine in children and adolescents < 13 years treated with 1HP, use in pregnancy *(139)* and interactions between rifamycin-containing regimens and other medicines, particularly ART in adults and children. In addition, the durability of protection provided by different TPT regimens, including long-acting injectables *(140,141)*, should be evaluated in settings endemic for TB, including the efficacy of repeated courses of TPT and, if effective, the optimal interval between treatment courses. Studies of the preferences of different stakeholders for different regimen characteristics would be helpful.

Monitoring of adverse events

Prospective randomized studies are required to determine the incremental benefits of routine monitoring of liver enzyme levels over education and clinical observation alone for preventing severe clinical adverse events, with stratification of the evidence by the population at risk. Programmatic data on maternal and pregnancy outcomes, possibly by trimester of exposure and including post-natal follow-up of the child, could supplement current knowledge about the safety of different TPT regimens when used in pregnancy.

Collection of programmatic data on adverse events and maternal and pregnancy outcomes, including post-natal follow-up of the child, would supplement current knowledge about the safety of levofloxacin TPT when used during pregnancy and breast-feeding.

Drug resistance and TPT

Programme-based surveillance systems and clinical studies should be conducted to monitor the risk for resistance to the medicines used in TPT. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data. Conversely, the impact on PMTPT of high levels of resistance among prevalent TB strains to isoniazid and/or rifamycins should be studied. Programme-based surveillance and specially designed studies should be conducted to monitor the emergence of clinically relevant resistance in TB bacilli and other bacterial flora to fluoroquinolones and other medicines used on a large scale for TPT.

Adherence to and completion of treatment

Carefully designed studies, including RCTs, are required to establish the effectiveness of context-specific interventions to improve adherence and completion of treatment. The studies should include specific risk groups, depending on resources and the health-system infrastructure, and address questions on integration of TPT into differentiated models of HIV service delivery. Use of digital technology to improve adherence is an important area. Further research is required on the effectiveness of self-administration of the 3-month regimen of weekly rifapentine plus isoniazid.

Studies on the effectiveness of context-specific interventions to enhance adherence and completion of treatment, such as self-administration with and without digital technology to ensure adherence, will be helpful. Implementation research on context-specific barriers and facilitators is necessary for TPT to MDR/RR-TB, to explore dimensions for which the evidence is often sparse, such as acceptability, feasibility, equity and resource use.

Cost–effectiveness

Research should be conducted on service delivery models for TPT in order to lower costs, improve equity and optimize the follow-up of people exposed to TB and MDR/RR-TB, whether or not they received fluoroquinolones, in terms of duration, monitoring approaches and frequency of visits. Such evidence could guide optimization of contact-tracing strategies in households and the delivery of public health interventions for common modifiable risks of affected people, such as use of tobacco, drugs and alcohol.

Preventive treatment for contacts of people with MDR/RR-TB

The strong recommendation for use of TPT for MDR/RR-TB should not be used as a justification for stopping trials or create ethical impediments to such research. RCTs with adequate power are still necessary to update the recommendation on TPT for contacts of people with MDR/RR-TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as people with HIV. The composition, dosage and duration of TPT regimens for MDR/RR-TB could be further optimized, and the potential role of newer agents with good sterilization properties should be investigated. Regimens that remain effective in the presence of fluoroquinolone resistance should also be studied. The effectiveness and safety of TPT for contacts of people with MDR/RR-TB should be evaluated under operational conditions. Further evidence on the risk for progression to TB disease of contacts of people with MDR/RR-TB will be important for understanding the benefits of TPT.

TPT regimens for MDR/RR-TB that are shorter than 6 months and have a good safety profile in childhood, pregnancy and in the presence of co-morbidities or a risk of drug–drug interactions will be essential. Pregnancy should not be an absolute exclusion criterion in such studies.

Studies are also necessary on the long-term efficacy of TPT regimens for MDR-TB, especially in settings with a high risk of MDR-TB re-exposure. The efficacy of fluoroquinolones and other TPT in areas with high levels of resistance in TB strains to the medications used as TPT should be monitored. Regimens that remain effective in the presence of fluoroquinolone-resistant TB strains should be identified for areas of high fluoroquinolone resistance.

Programme management

Continued epidemiological research should be conducted to determine the burden of TBI in specific geographical settings and risk groups, as a basis for nationally and locally tailored interventions, including integrated community approaches. Implementation research on context-specific barriers and facilitators is necessary for different TPT regimens to explore dimensions on which little evidence is available, such as acceptability, feasibility, equity and resource use. Research should also be conducted on service delivery models, including differentiated (community) models for TPT, to improve management, including the provision of additional interventions for tobacco smokers and harm reduction services for people who use drugs or who engage in harmful use of alcohol and for people in prison. Operational research on household implementation models to improve uptake of TPT could increase the effectiveness and efficiency of interventions. Future evidence from trials could guide optimization of contact-tracing strategies in households and elsewhere. Tools should be developed and assessed to facilitate monitoring and evaluation of PMTPT to improve future global guidance.

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Annex 1. Recommendations in the WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment, second edition (2024) and in the previous edition (2020)

The key changes in the current second edition of these guidelines are highlighted in Box 1, after the Executive summary.

Table A1.1. Recommendations in the 2020 guidelines and recommendations in the current update (2024)

Recommendations in the 2020 guidelines	***Recommendations in the current update (second edition)***
1.1. Identifying populations for LTBI testing and TB preventive treatment	**1.1. Identifying populations for TB preventive treatment**
People living with HIV	*People with HIV*
1. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable.	1. Adults and adolescents living with HIV who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if testing for TB infection is unavailable. *(language editing)*
2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.	2. Infants aged < 12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(language editing)*

Recommendations in the 2020 guidelines	***Recommendations in the current update (second edition)***
3. Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.	3. Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(language editing)*
4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.	4. All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(no change)*
Household contacts (regardless of HIV status)	*Household contacts of people with TB (regardless of HIV status)*
5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable.	5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if testing for TB infection is unavailable. *(language editing)*
6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.	6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(language editing)*
7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.	*(replacement with Recommendation 21 under section* ***1.4. TB preventive treatment options).***
Other people at risk	*Other people at risk*
8. People who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for LTBI.	7. People who are initiating anti-tumour-necrosis factor treatment, or receiving dialysis, preparing for an organ or haematological transplant or have silicosis should be systematically tested and treated for TB infection. *(language editing)*

Recommendations in the 2020 guidelines	***Recommendations in the current update (second edition)***
9. Systematic LTBI testing and treatment may be considered for prisoners, health workers, immigrants from countries with a higher TB burden, homeless people and people who use drugs.	8. Systematic testing and treatment for TB infection may be considered for prisoners, health workers, immigrants from countries with a higher TB burden, homeless people and people who use drugs. *(language editing)*
10. Systematic LTBI testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.	*(recommendation withdrawn)*
1.2. Algorithms to rule out active TB disease	**1.2. TB screening and ruling out TB disease**
11. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status. 12. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded.	10. Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease. Those who report any of these symptoms may have TB, should be evaluated for TB disease and other diseases and should be offered TB preventive treatment if TB disease is excluded, regardless of their antiretroviral treatment status. *(recommendations 11 and 12 from the 2020 WHO TPT guidelines merged to integrate the pathway of implementation of both screening and TPT as one recommendation)*
13. Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings.	11. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease. (*recommendation 13 from the 2020 guidelines updated with the one from the 2021 WHO TB screening guidelines*)
	12. Among adults and adolescents living with HIV, C-reactive protein at a cut-off of > 5 mg/L may be used to screen for TB disease. *(recommendation added from the 2021 WHO TB screening guidelines)*
	13. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease. *(recommendation added from the 2021 WHO TB screening guidelines)*

Recommendations in the 2020 guidelines	***Recommendations in the current update (second edition)***
14. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.	9. Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age. *(no change)*
15. The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other risk groups before preventive treatment.	14. Among HIV-negative household contacts aged ≥ 5 years and other risk groups, the absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out TB disease before TB preventive treatment. *(language editing)*
	15. Among individuals aged ≥ 15 years in populations in which TB screening is recommended, systematic screening for TB disease may be conducted with a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination. *(recommendation added from the 2021 WHO TB screening guidelines)*
	16. Among individuals < 15 years who are close contacts of a person with TB, systematic screening for TB disease should be conducted with a symptom screen of any one of cough, fever or poor weight gain; or chest radiography; or both. *(recommendation added from the 2021 WHO TB screening guidelines)*
1.3. Testing for LTBI	**1.3. Testing for TBI**
16. Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI.	17. Either a tuberculin skin test (TST) or interferon-γ release assay (IGRA) can be used to test for TB infection. *(language editing)*
	18. *Mycobacterium tuberculosis* antigen-based skin tests (TBST) may be used to test for TB infection. (*recommendation added from the 2022 WHO guidelines on tests for TB infection*)

Recommendations in the 2020 guidelines	***Recommendations in the current update (second edition)***
1.4. TB preventive treatment options	**1.4. TB preventive treatment options**
17. The following options are recommended for the treatment of LTBI regardless of HIV status : 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives.	*TB preventive treatment with isoniazid or rifamycins* 19. The following TB preventive treatment options are recommended regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin. 20. The following alternative TB preventive treatment options may be used regardless of HIV status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin. *(recommendation 17 from the 2020 WHO TPT guidelines has been split into two in the second edition: recommendation 19 for regimens which are strongly recommended and recommendation 20 for alternative regimen options that are conditionally recommended.)*
18. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.	*(recommendation withdrawn)*
(replacement of recommendation 7 from the 2020 WHO TPT guidelines under previous section ***1.1. Identifying populations for LTBI testing and TB preventive treatment)***	*TB preventive treatment with levofloxacin* 21. In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, 6 months of daily levofloxacin should be used as TB preventive treatment.

Annex 2. Methods and expert panels

WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment, second edition

A2.1 Scope and objectives

The WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment make recommendations for the four milestones of the cascade of preventive care, namely, identification of risk groups, TB screening and ruling out TB, testing for TBI and choice and administration of the TPT regimen. The second edition of the TPT guidelines covers the same milestones.

Since the previous update of the guidelines on TPT, in 2020 *(1)*, further developments have occurred that affect TPT policy. They include revision of WHO guidance on screening for TB disease and new modalities for testing for TBI *(2,3)*. In addition, by 2023, two landmark trials of TPT for contacts of patients with MDR-TB had been completed *(4,5)*. In view of this new information and continued demand by Member States for guidance on protecting people at risk of TB, a second edition of the TPT guidelines has been prepared that includes the latest evidence. The objectives of this second edition were to:

- review the latest evidence for TPT in cases of MDR-TB and revise the respective recommendation accordingly;
- align the guideline recommendations on ruling out TB and testing for TBI to the WHO recommendations on screening and diagnostics that have been revised since 2020; and
- enhance the operational guidance with more practical details on dosing schedules, support for adherence to medication and minimizing the toxicity of current regimens.

The aim of the revised guidelines is to support more effective global scaling up of TPT and to contribute to ending the global TB epidemic. These updated guidelines will allow users to choose the management approach best suited for all target groups in each context. It also provides a sound basis for the development or updating of national guidelines for TPT, which is based on the epidemiology of TB and the health-care delivery system in each country. Furthermore, the guidelines address the request by Member States for a comprehensive policy and operational guidance for programmatic management of TPT. The guidelines are being issued with an updated operational handbook containing complementary, practical details for implementation.

A2.2 Methods used to develop the guidelines

In accordance with the process recommended by the Guideline Review Committee *(6)*, three expert groups were established: a Guideline Steering Group, composed of WHO staff; the GDG, comprising external content experts, national TB programme managers, other implementers, academics, researchers and representatives of patients and civil society, led by a guideline methodologist; and the ERG, composed of peer-reviewers.

The WHO Guideline Steering Group prepared the background document for the guidelines, which detailed the PICO question that would define the main evidence-based recommendation that was to be updated; the trial data and evidence review required; draft changes to the wording of existing recommendations and accompanying remarks to improve clarity and implementation of the guidance; and the composition of the expert panels. The scoping document was submitted to the Guideline Review Committee and approved in May 2023. Information about the GDG members was placed on a public website in November 2023 (https://cdn.who.int/media/docs/default-source/hq-tuberculosis/biographies_gdg_tpt_2023.pdf?sfvrsn=95176f7e_3).

GDG meetings were conducted as 3-h virtual webinars on 4–6 December 2023, and three virtual preparatory meetings of the GDG were held in September, October and November 2023 to discuss the procedures to be followed and to review the preliminary data. Evidence summary tables were drafted for the PICO question by the guideline methodologist with the GRADE approach and circulated to the group before the webinars. The meetings were chaired by a technical expert, while the guideline methodologist facilitated the discussions to reach consensus, which was defined as unanimous or majority agreement. The GDG agreed in advance that, if unanimity was not achieved for a recommendation to be made, the members of the GDG would vote and that a majority of 60% or more of voting members would be necessary to accept a recommendation. If the vote reached this threshold but was less than 70%, the recommendation would be conditional. The estimates of effect and the judgements on the quality of evidence were reviewed by the GDG during the online discussions. GRADE evidence-to-decision tables were used to guide discussions of benefits and harm, the quality of evidence, cost, feasibility, acceptability, equity, values and preferences. The direction of the recommendation and its strength (strong or conditional) were determined by these factors. GRADEpro was used to document the decisions made *(7)*.

A2.3 Scoping and PICO question

The recommendations in the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment, second edition* are structured around 10 PICO questions (Table A2.1).

Table A2.1. PICO questions for the WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment, second edition

PICO 1: What is the prevalence of TBI, risk of progression to TB disease and cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries?
PICO 2: What is the accuracy of WHO symptomatic screening to exclude TB disease in individuals with HIV on ART?
PICO 3: What is the accuracy of symptomatic screening and/or CXR to exclude TB disease in contacts of people with pulmonary TB without HIV in high TB incidence countries?
PICO 4: Could IGRAs be used as an alternative to TSTs to identify individuals at greatest risk of progression from TBI to TB disease in high TB incidence settings?
PICO 5: Should 3-month daily rifampicin plus isoniazid (3RH) be offered as a preventive treatment option for children and adolescents < 15 years of age as an alternative to 6 or 9 months isoniazid monotherapy in high TB incidence countries?
PICO 6: In people of all ages at risk of TB disease, does a 4-month daily rifampicin regimen safely prevent TB disease as compared with other recommended TPT regimens?
PICO 7: In people of all ages at risk of TB disease, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease as compared with other recommended TPT regimens?

PICO 8: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of TBI in high TB incidence countries?
PICO 9: In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens?
PICO 10: Should 6 months of levofloxacin, another regimen or no TPT be recommended for people in contact with patients with MDR/RR-TB?

Evidence retrieved for the second edition of the TPT guidelines was primarily to answer PICO question 10 (Table A2.2). The answers to this question were intended to be used to update the original conditional recommendation on TPT of MDR-TB, which was based on very low certainty of the estimates of effect, namely: "In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and sound clinical justification".

Table A2.2. PICO question on TB preventive treatment for contacts exposed to MDR/RR-TB: *Does tuberculosis preventive treatment with levofloxacin improve outcomes in contacts exposed to multidrug- or rifampicin-resistant tuberculosis when compared with other regimens or no treatment?*

P	Household and other contacts of a person with MDR-/RR-TB Sub-populations: age-groups (child, adolescent, adult); people living with HIV
I	6-month daily levofloxacin
C	Other recommended TB preventive treatment regimen: isoniazid daily for 6, 9 or 36 months;, 3 months of weekly isoniazid plus rifapentine; 1 month of daily isoniazid plus rifapentine; 3 months of daily isoniazid plus rifampicin; 4 months of rifampicin; ethionamide/protionamide; other tuberculosis drugs; no TBY (placebo)
O	TB incidence, mortality (TB, any), adverse events, treatment completion, emergence of additional fluoroquinolone resistance in TB strains, emergence of additional fluoroquinolone resistance in microbiome other than TB (e.g. gut flora)

Once the PICO question had been finalized by the GDG, a list of potential outcomes of interest was circulated to all members to score the importance of each outcome on an incremental scale of 1–9: 1–3: "not important"; 4–6: "important"; and 7–9: "critical". The mean of the scores for each outcome was then used to prioritize those for evidence summarization and for GDG discussions. All outcomes were scored by the GDG as "critical" or "important" (see also the GRADE tables in annexes 3 and 4).

Most of the evidence reviewed for the main outcomes of this PICO question was from two randomized, placebo-controlled trials on use of levofloxacin vs no treatment *(4,5)*. A literature search was also conducted for other published studies that could inform the recommendation. In addition, a survey of users in national TB programmes and of people in contact with MDR-TB was conducted on various aspects of implementation (e.g. acceptability, feasibility, impact on equity).

In addition to the review of evidence for the PICO question, the previous recommendations were reviewed for clarity of wording, applicability in different settings and alignment with other WHO guidance. The structure used in the first edition of the guidelines, in 2020, which was the cascade of programmatic management of TPT, was retained. This is: identification of populations at risk (adults and children living with HIV, adult and child contacts of people with TB and other risk groups); ruling out TB disease; testing for TBI; providing treatment (including managing adverse events and supporting adherence) and monitoring and evaluation. The text of the recommendation is followed by summaries

of the evidence (justification), discussion of their rationale and considerations on implementation, key subgroups, monitoring, evaluation and research gaps. Recommendations that remained valid were retained, with or without slight rewording (see Annex 1, above). Two that were considered obsolete by the GDG were withdrawn. Relevant recommendations from two WHO guidelines in the consolidated series that were issued in 2021 and 2022 were included in this second edition of the guidelines. (For methods used in previous guidelines, see the respective documents and related annexes *(1–3,8)*.)

The guidelines and the supporting documents were reviewed and endorsed by all GDG members. Remarks from the ERG were assessed by the WHO Guideline Steering Group and included in the guidelines. Final approval of the guidelines by the Guideline Review Committee was received on 28 May 2024.

A2.4 Certainty of the estimates of effect and strength of the recommendations

The certainty of the estimates of effect (or the quality of evidence) and the strength of the recommendations were assessed with the GRADE method *(9)*. Certainty of evidence was defined as the degree of confidence that the estimates of effect (desirable or undesirable) are close to the actual effects of interest. The usefulness of an estimate of effect depends on the degree of confidence in that estimate: the higher the certainty of the evidence, the more likely it is that a strong recommendation can be made. WHO guideline development is based on specific criteria for assessing the characteristics of a study, such as within-study bias (methodological quality), consistency, precision, directness or publication bias. Most of the evidence reviewed by the GDG in December 2023 was from two RCTs, which was considered to be of high certainty for five of the eight outcomes and moderate, low or very low for one outcome each (see annexes 3 and 4). An assessment of the risk of bias was conducted by the guidelines methodologist.

The strength of a recommendation reflects the degree of confidence of the GDG that the desirable effects outweigh the undesirable effects. The desirable effects include beneficial health outcomes (e.g. prevention and early diagnosis of TB, reduced TB-related morbidity and mortality), a smaller burden of TB and greater savings. The undesirable effects included harm, a greater burden and greater cost. The "burdens" included adherence to recommendations by programmes, patients and caregivers – formal or informal – such as more frequent tests and taking additional medications.

The certainty of the estimates of effect (quality of evidence) was categorized into four levels:

- *High*: The GDG is very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: The GDG is moderately confident that the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- *Low*: The confidence of the GDG in the effect estimate is limited: the true effect may be substantially different.
- *Very low*: The GDG has very little confidence in the effect estimate: the true effect is likely to be substantially different.

The recommendations are either strong or conditional.

A *strong recommendation* is one for which the GDG was confident that the desirable effects of adherence to it would outweigh the undesirable effects. The recommendation could be either in favour of or against an intervention.

A *conditional recommendation* is one for which the GDG concluded that the desirable effects of adherence to it would probably outweigh the undesirable effects; however, the GDG was not confident about the trade-off. The reasons for lack of confidence included: absence of high-quality evidence (few data to support the recommendation); imprecise estimates of benefit or harm (new evidence might change the ratio of risk to benefit); uncertainty or variation in the value of the outcomes for

different individuals (applicable only to a specific group, population or setting); and small benefits or benefits that might not be worth the cost (including the cost of implementing the recommendation).

The strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, resource use, equity considerations, acceptability and the feasibility of implementing the intervention. The strength of a recommendation has specific implications for individuals affected by these guidelines (Table A2.3).

Table A2.3. Implications of the strength of a recommendation for different stakeholders

Perspective of	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would accept the recommended course of action and only a small proportion would not. Individuals are unlikely to require aid in making decisions consistent with their values and preferences.	The majority of individuals in this situation would accept the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for different patients and that patients should be assisted in arriving at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and the involvement of various stakeholders.

A2.5 Publication, implementation, evaluation and expiry

These guidelines were prepared in accordance with the requirements of the Guideline Review Committee. They are being published for free download on the WHO institutional repository for information sharing *(10)* and the WHO TB Knowledge Sharing Platform *(11)* as part of the modular series of WHO consolidated guidelines on TB. The documents will also be communicated widely at international and regional conferences and meetings of programme managers in all regions. They are accompanied by an operational guide containing practical details to support programmatic implementation of the revised recommendations *(12)*.

National programmes will be supported by WHO and technical and funding partners in preparing national plans for programmatic management of TPT, including prioritization of groups at high risk according to local epidemiology and the characteristics of the health system. Implementers should create a conducive policy and programmatic environment, including national and local policies and standard operating procedures to facilitate implementation of the recommendations in these guidelines. This should include promoting universal health coverage and offering public financing for TPT. Furthermore, dedicated resources should be allocated, including for staff development and service delivery in the community. Training of front-line health-care staff and students in critical areas, such as identification of populations at risk, administering tests for TBI, choosing TPT, counselling and management of adverse drug reactions, is important. National programmes should ensure

meaningful engagement with affected populations, their communities, the private sector, other relevant health programmes and ministries in both planning and implementing the interventions. The process should facilitate concordance with other guidance on relevant risk factors for TB, such as diabetes, undernutrition and tobacco smoking, and access to comprehensive care for people with these co-existing risks.

The uptake of these WHO recommendations will be monitored during annual data collection for WHO Global TB Data Monitoring *(13)*. WHO will update the guidelines 5 years after their publication or earlier if new evidence becomes available that necessitates a revision.

A2.6 Composition of the Guideline Development Group and the External Review Group[6]

The following experts composed the GDG and ERG for the second edition of the TPT guidelines (Tables A2.4 and A2.5).

Table A2.4. Guideline Development Group, 2023–2024

Name	Gender	Area of expertise	WHO region
Mênonli Adjobimey	F	National TB programme; trials	African
Rolando Cedillos	M	Content and clinical expertise	Americas
Ana Ciobanu	F	Content	European
Alexander Kay	M	Paediatrics; trials	African
Naira Khachatryan	F	National TB programme	European
Amir Khan	M	Private sector; civil society	Eastern Mediterranean
Senia Rosales Klintz	F	Surveillance	European
Blessina Kumar	F	Gender, equity and rights	Southeast Asia
Natalia Litvinenko	F	National TB programme	European
Nasehi Mahshid	F	National TB programme	Eastern Mediterranean
Charisse Malbacias	F	National TB programme	Western Pacific
Alberto Matteelli	M	Content and clinical expertise	European
Norbert Ndjeka (Chair)	M	National TB programme	African
Nicole Salazar-Austin	F	Paediatrics; trials	Americas
Susan Swindells	F	Research and trials	Americas
Stavia Turyahabwe	F	National TB programme	African
Paran Winarni	F	Gender, equity and rights	Southeast Asia
Lawrence Mbuagbaw	M	Guideline methodologist	Americas

[6] See Acknowledgements in the main text for affiliations and countries of experts.

Table A2.5. External Review Group, 2023–2024

Name	Gender	Area of expertise	WHO region
Helen Ayles	F	Research and trials	European
Anurag Bhargava	M	Research and trials	Southeast Asia
Gavin Churchyard	M	Research and trials	African
Marie Diaz	F	National TB programme	Western Pacific
Raquel Duarte	F	Content and clinical expertise	European
Amita Gupta	F	Research and trials	Americas
Anthony D Harries	M	Content	European
Nino Lomtadze	F	Content	European
Lindiwe Mvusi	F	National TB programme	African
Ruslan Malyuta	M	Paediatrics	Americas
Giovanni B. Migliori	M	Content	European
Anastasia Samoilova	F	National TB programme	European
Alena Skrahina	F	National TB programme	European
Carrie Tudor	F	Content	Americas
Valentina Vilc	F	National TB Programme	European

A2.7 Declarations of interests and management of potential conflict

The members of the GDG and ERG for the second edition of the TPT guidelines completed a WHO declaration of interests form in 2023. All the declarations were evaluated by the WHO Guideline Steering Group for any financial conflict of interest that might warrant exclusion from membership or from certain discussions of the GDG. The completed forms were summarized and presented to all GDG members on the first day of the meeting, at which time the members were requested to update their declarations. Intellectual conflict of interest was not considered a motive for exclusion from the GDG, as expertise on a topic was considered an important criterion for selection, and the diversity and representation in the Group was wide enough to balance any individual member's intellectual interest.

Guideline Development Group

The following GDG members declared no interests that could conflict with the objectives of the guidelines: Mênonli Adjobimey, Ana Ciobanu, Naira Khachataryan, Amir Khan, Blessina Kumar, Natalia Litvinenko, Charisse Malbacias, Nasehi Mashid, Alberto Matteelli, Norbert Ndjeka (chair), Stavia Turyahabwe, Paran Winami.

The following GDG members declared interests that were judged not to conflict with the objectives of the meeting:

Rolando Cedillos declared consultancy payment of US$ 3000 from the Pan American Health Organization in 2022.

Alexander Kay declared ongoing supplies of discounted Xpert MTB/RIF cartridges to Baylor Children's Foundation in Eswatini from Cepheid for a value of about US$ 2000. He also declared current funding from the US Centers for Disease Control and Prevention to Baylor College of Medicine for about US$ 5 million for a study on support for adherence to TPT with 3HP vs 6H.

Senia Rosales Klintz reported employment by the European Centre for Disease Prevention and Control.

Nicole Salazar-Austin reported research support equivalent to 75% of her salary from the US National Institutes of Health in 2019–2023, which was unrelated to drug-resistant TB treatment or prevention; and consulting for Rutgers Global TB Institute in 2022 (value US$ 5000) for the CHIP-TB project.

Susan Swindells reported current travel support of about US$ 2000 from the US National Institutes of Health and research support until 2022 (about US$ 40 000 salary support and US$ 4000 travel support) for her role as protocol chair of the BRIEF-TB trial on 1HP and to serve as a member of the NIH Adult & Adolescent Antiretroviral Treatment Guidelines Panel, TB section. She also reported research support to her institution from ViiV Healthcare up to 2022 (US$ 10 000 in salary support).

Lawrence Mbuagbaw, the guideline methodologist, reported support from Janssen Pharmaceuticals in 2018–2020 for analysing data on use of bedaquiline for treatment of MDR-TB in South Africa (US$ 150 000).

The following GDG member declared interests that were judged to conflict with the objectives of the meeting and was recused from the meeting: Hoa Binh Nguyen reported being a team member of the V-QUIN trial and receiving payment of about US$ 100 per month from the Woolcock Institute in Australia for this work.

External Review Group

The following ERG members declared no interests that could conflict with the objectives of the guidelines: Anurag Bhargava, Marie Diaz, Anthony D. Harries, Nino Lomtadze, Lindiwe Mvusi, Ruslan Malyuta, Giovanni B. Migliori, Anastasia Samoilova, Alena Skrahina, Carrie Tudor and Valentina Vilc.

The following ERG members declared interests that were judged not to conflict with the policy of WHO or the objectives of the meeting:

Helen Ayles reported in-kind support to her research group of test kits for the diagnosis of TBI from BD Biosensor (valued at about US$ 5000), Serum Institute of India (valued at about US$ 2000) and Qiagen (valued at about US$ 2000). She also declared support to her research group from a Stop TB Partnership TB Reach grant for scaling up of TPT in conjunction with testing for TBI (US$ 699 734).

Gavin Churchyard reported research support from Sanofi to his employer, Aurum Institute, as donated rifapentine and isoniazid for the WHIP3TB trial (valued at about US$ 350 000). He declared participation in a Sanofi advisory board on rifapentine for TPT, without travel support or payment. In addition, he reported a grant from USAID via KNCV/Challenge TB grant for the WHIP3TB trial (about US$ 14.2 million). He further reported a donation of rifapentine from Lupin Ltd to IMPAACT4TB studies (valued at US$ 300 000) and an honorarium from Janssen Pharmaceuticals for participating in an advisory board for developing long-acting injectable for bedaquiline (US$ 1100).

Amita Gupta reported research grants to her university from US National Institutes of Health, UNITAID, the US Centers for Disease Control and Prevention, the US Agency for International Development and Wyncote Foundation (unspecified amounts).

Raquel Duarte reported the following grants: 2021 (current) UNITE4TB: Academia and Industry innovation and treatment for Tuberculosis. (H2020 UNITE4TB 101007873) [1 June 2021–31 May 2028] [national principal investigator]; 2019 (current) – EUSAT-RCS: European–Latin American TB Research Collaboration Network (H2020 EUSAT-RCS 823890) [1 April 2019–18 March 2024] [national principal investigator]; 2018–2022, UrbanTB: from symptoms to diagnosis of urban tuberculosis

considering individual and contextual factors. What are the determinants and critical points of this delay's pathway? (FCT POCI-01–0145-FEDER-031346, PTDC/SAL-PUB/31346/2017) [1 October 2018–30 September 2022] [co-principal investigator]. In addition, she has been working as a TB consultant for the Portuguese national and regional TB programme and is also a Member of the TB Disease Network Coordination Committee of the European Centre for Disease Prevention and Control.

Evidence reviewers

The evidence reviewers undertook data collection and summarization and provided the estimates for the evidence summaries but did not participate in formulating the recommendations for policy.

The following evidence reviewers declared no interests that could conflict with the objectives of the guidelines: Stephanie Law and Harsimren Sidhu.

The following reviewer declared interests that were judged not to conflict with the policy of WHO or the objectives of the meeting: Richard (Dick) Menzies declared research support from the Canadian Institutes of Health Research of about CAN$ 1.1 million per year in 2015–2023. The work was not associated with TPT for MDR-TB.

For the composition and declarations of interest of the GDG and other expert groups involved in formulation of earlier recommendations cited in these WHO guidelines, see the previous guidelines and related annexes *(1–3,8)*.

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Annex 3. GRADE summary of evidence tables

Older terminology used in the context of TPT, such as latent TB infection (LTBI) and active TB, has been retained in the original text of the tables.

Contents

PICO 1: What is the prevalence of TB infection, the risk of progression to TB disease and the cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries? 63

PICO 2: What is the accuracy of WHO symptomatic screening to exclude TB disease in individuals with HIV on antiretroviral treatment (ART)? 69

PICO 3: What is the accuracy of symptomatic screening and/or chest x-ray to exclude TB disease in contacts of people with pulmonary TB without HIV in high TB incidence countries? 70

PICO 4: Could interferon-γ release assays be used as an alternative to tuberculin skin tests to identify individuals at greatest risk of progression from TB infection to TB disease in high TB incidence settings? 72

PICO 5: Should 3-month daily rifampicin plus isoniazid (3RH) be offered as a preventive treatment option for children and adolescents <15 years of age as an alternative to 6 or 9 months' isoniazid (INH) monotherapy in high TB incidence countries? 75

PICO 6: In people of all ages at risk of TB disease, does a 4-month daily rifampicin regimen safely prevent TB disease as compared with other recommended TB preventive treatment regimens? 77

PICO 7: In people of all ages at risk of TB disease, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease as compared with other recommended TB preventive treatment regimens? 82

PICO 8: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of TB infection in high TB incidence countries? 87

PICO 9: In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens? 91

PICO 10: Should 6 months of levofloxacin rather than other regimens or no TPT be recommended for people in contact with patients with MDR/RR-TB? 94

PICO 1: What is the prevalence of TB infection, the risk of progression to TB disease and the cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries?

Is the prevalence of TB disease and TB infection higher among household contacts without HIV than in the general population in different age groups in high TB incidence countries?

Quality assessment						No. TBI+/No. tested		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
Age groups compared: 5–10 years vs 0–5 years											
14 *(1–14)*	Cross-sectional	Not serious[a,b]	Serious[c]	Not serious	Not serious[d]	2265/8507	1298/9526	1.62 (1.25 ; 2.11)	85.1 (34.2 ; 151.1)	Moderate	Important
Age groups compared: 10–15 years vs 0–5 years											
11 *(1,3,5,7–14)*	Cross-sectional	Not serious[e]	Serious[f]	Not serious	Not serious[g]	2616/6782	1093/9005	2.33 (1.55 ; 3.50)	161.6 (67.2 ; 303.3)	Moderate	Important
Age groups compared: 5–15 years vs 0–5 years											
16 *(3,5,8, 10,12,15–25)*	Cross-sectional	Serious[h]	Serious[i]	Not serious	Not serious[j]	3709/8772	1605/5095	1.32 (1.11 ; 1.56)	99.7 (34.9 ; 176.5)	Low	Important
Age groups compared: > 15 years vs 0–5 years											
19 *(3–5,8–10, 12–14,16,17, 19,20–26)*	Cross-sectional	Not serious[k]	Serious[l]	Not serious	Not serious[m]	13218/21962	1979/6763	2.04 (1.53 ; 2.63)	293.9 (155.1 ; 475.7)	Moderate	Important

[a] Potential selection bias in *(2)*, as only 69% of participants were household contacts.
[b] Potential misclassification: Eight studies *(3–5,7,10,11,13,14)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
[c] High heterogeneity among studies (I^2 = 94%) probably due to difference in background TB incidence. Risk ratios of two studies *(1,5)* showed opposite effect.
[d] Small sample size in *(5)* (n < 50).
[e] Potential misclassification: Seven studies *(3,5,6,10,11,13,14)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
[f] High heterogeneity among studies (I^2 = 97%) probably due to differences in background TB incidence. Risk ratio of one study *(5)* showed opposite effect.
[g] Wide confidence interval of pooled risk ratio. Small sample sizes in *(5)* (n < 50) and *(12)* (n < 100).
[h] Potential selection bias in *(15)*, as only 89% of participants were household contacts.
[i] High heterogeneity among studies (I^2 = 93%) probably due to differences in background TB incidence. Risk ratios in three studies showed opposite effects *(5,19,21)*.
[j] Small sample size in *(5)* and *(18)* (n < 50).
[k] Potential misclassification: Ten studies *(3–5,10,13,14,20,21,23,26)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data to calculate the number of household contacts with active TB per age stratum.
[l] High heterogeneity among studies (I^2 = 98%) probably due to differences in background TB incidence.
[m] Small sample sizes in *(5)* and *(26)* (n < 100).

Development of TB disease in household contacts with TB infection in high TB incidence countries

Quality assessment							No of contacts (active TB/no. TBI)		Effect		Quality	Importance
No, of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
Age groups compared: 5–15 years vs 0–5 years												
4 *(8,13,15,16)*	Cohort	Not serious	Not serious	Serious[a]	Not serious	Serious[b]	54/1329	73/630	0.28 (0.12 ; 0.65)	83.8 (40.3 ; 102.3)	Low	Critical
Age groups compared: > 15 years vs 0–5 years												
3 *(8,13,16)*	Cohort	Not serious	Not serious	Serious[c]	Not serious	Not serious	186/4746	73/595	0.22 (0.08 ; 0.60)	95.5 (49.1 ; 112.6)	Moderate	Critical

Because of the small number of studies in the other categories, only data from studies with a follow-up of 1–2 years in high TB incidence countries are presented in the table.

[a] Serious inconsistencies due to heterogeneity (I^2 = 71%): One study showed an increased risk in the age group 5–15 years. This was not observed in the other studies.

[b] Small number of events.

[c] High heterogeneity among studies probably due to differences in background TB incidence and methods used to diagnose active TB (I^2 = 89.3%).

Cumulative prevalence of TB disease in household contacts irrespective of baseline TB infection status in high TB incidence countries

Quality assessment							No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95%CI)		
Age groups compared: 5–15 years vs 0–5 years												
6 *(8,13,15, 16,18,27)*[a]	Cohort	Not serious	Not serious	Serious[b]	Not serious	Not serious	131/4389	203/2903	0.39 (0.18 ; 0.85)	42.9 (10.6 ; 57.6)	Moderate	Important
Age groups compared: >15 years vs 0–5 years												
4 *(8,13,16,27)*	Cohort	Not serious	Not serious	Not serious	Not serious	Not serious	417/10856	192/2764	0.68 (0.56 ; 0.83)	22 (12.1 ; 30.3)	High	Important

Owing to the small number of studies in the other categories, only data from studies with a follow-up of 1–2 years in high TB incidence countries are presented in the table.

[a] One outlier *(28)* was excluded because of uncertainty about the cases included (co-prevalent vs incident cases).

[b] High heterogeneity among studies (I^2 = 87.6%), probably due to the difference in background TB incidence.

TB disease in household contacts with TB infection and in the general population in high TB incidence countries (12 months)

Active TB disease in household contacts with TBI infection in high TB incidence countries: Comparison with the general population (follow-up of 12 months)											
Quality assessment						No. of contacts (active TB/no. TBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population[a]	RR (95% CI)	Absolute per 1000 (95% CI		
Comparison: Household contacts aged 0–5 years vs general population											
2 *(8,15)*	Cohort	Serious[b]	Serious[c]	Not serious	Very serious[d]	0/35 32/230	41/10 000 13/10 00	24.32 (0.73 ; 811.02)	63 (–0.7 ; 2187.1)	Very low	Critical
Comparison: Household contacts aged 5–9 years vs general population											
1 *(8)*	Cohort	Serious[b]	Not serious	Not serious	Serious[f]	12/298	13/10 000	30.98 (14.26 ; 67.31)	39 (17.2 ; 86.2)	Low	Critica
Comparison: Household contacts aged 10–14 years vs general population											
1 *(8)*	Cohort	Serious[b]	Not serious	Not serious	Serious[f]	26/363	13/10 000	55.1 (28.55 ; 106.33)	70.3 (35.8 ; 136.9)	Low	Critica
Comparison: Household contacts aged 5–15 years vs general population											
2 *(8,15)*	Cohort	Serious[b]	Not serious[e]	Not serious	Serious[f]	4/67 38/661	41/10 000 13/10 00	27.13 (17.47 ; 54.07)	70.5 (21.3 ; 220.7)	Low	Critical
Comparison: Household contacts aged > 15 years vs general population											
1 *(8)*	Cohort	Serious[c]	Not serious	Not serious	Serious[f]	155/3879	13/10 000	30.74 (17.46 ; 54.07)	38.7 (21.4 ; 69)	Low	Critical

[a] TBI does not apply to the general population.
[b] Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and the study population differed (general population of all ages versus a specific age group).
[c] High heterogeneity among studies (I^2 = 83.9%), probably due to differences in background TB incidence.
[d] Serious imprecision with a wide confidence interval for the effect estimates, probably due to small study size and number of outcome events.
[e] I^2 = 72.5%, indicating moderate heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.
[f] Few events and wide CI.

TB disease in household contacts with TB infection compared with general population in high TB incidence countries (24 months)

Active TB disease in households of contacts with TBI infection in high TB incidence countries Comparison with the general population (follow-up ≤ 24 months)[a]											
Quality assessment						No of contacts (active TB/no. TBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General pop[b]	RR (95% CI)	Absolute per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
3 *(8,15,16)*	Cohort	Serious[c]	Serious[d]	Not serious	Serious[e]	0/35 26/320 32/230	82/10 000 41/10 000 26/10 000	22.87 (7.65 ; 68.63)	108.6 (33 ; 334.6)	Very low	Important
Comparison: Household contacts aged 5–9 years vs general population											
1 *(8)*	Cohort	Serious[c]	Not serious	Not serious	Serious[e]	12/298	26/10 000	15.49 (7.89 ; 30.4)	37.7 (17.9 ; 76.4)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(8)*	Cohort	Serious[c]	Not serious	Not serious	Serious[e]	26/363	26/10 000	27.55 (16.16 ; 46.96)	69 (39.4 ; 119.5)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
3 *(8,15,16)*	Cohort	Serious[c]	Serious[f]	Not serious	Serious[e]	4/67 6/475 38/661	82/10 000 41/10 000 26/10 000	8.22 (2.3 ; 29.36)	35.8 (6.5 ; 140.8)	Very low	Important
Comparison: Household contacts aged over 15 years vs general population											
2 *(8,16)*	Cohort	Serious[c]	Not serious[g]	Not serious	Not serious	26/571 155/3879	41/10 000 26/10 000	13.35 (9.46 ; 18.83)	41.4 (28.3 ; 59.7)	Moderate	Important

[a] These comparisons included studies with a maximum follow-up of 24 months; therefore, TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring during 24 months.
[b] TBI does not apply to the general population.
[c] Ascertainment bias highly likely: TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group). TB incidence in the population was estimated by multiplying the yearly notification rate by a factor of 2.
[d] High heterogeneity between studies probably due to difference in background TB incidence (I^2 = 84.4%).
[e] Few events and wide CI.
[f] I^2 = 88.1%, indicating high heterogeneity probably due to difference in background TB prevalence; however, there is a trend across age groups and studies.
[g] I^2 = 16%.

TB disease in household contacts irrespective of TB infection status compared with general population in high TB incidence countries (12 months)

Cumulative prevalence of active TB in household contacts irrespective of baseline TBI status in high TB incidence countries Comparison with the general population (follow-up of 12 months)											
Quality assessment						No. of contacts (active TB/total)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General pop	RR (95% CI)	Absolute risk per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
3 *(8,15,18)*	Cohort	Serious[a]	Not serious[b]	Not serious	Serious[c]	2/31 9/108 73/1791	28/10 000 41/10 000 13/10 000	25.86 (16.87 ; 39.66)	68 (43.4 ; 105.7)	Low	Important
Comparison: Household contacts aged 5–9 years vs general population											
1 *(8)*	Cohort	Serious[a]	Not serious	Not serious	Serious[c]	35/1464	13/10 000	18.39 (9.75 ; 34.68)	22.6 (11.4 ; 43.8)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(8)*	Cohort	Serious[a]	Not serious	Not serious	Serious[c]	45/1340	13/10 000	25.83 (13.97 ; 47.76)	32.3 (16.9 ; 60.8)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
3 *(8,15,18)*	Cohort	Serious[a]	Not serious[b]	Not serious	Serious[c]	8/102 16/161 80/2804	28/10 000 41/10 000 13/10 000	24.11 (16.89 ; 34.43)	63.2 (43.4 ; 91.4)	Low	Important
Comparison: Household contacts aged over 15 years vs general population											
1 *(8)*	Cohort	Serious[a]	Not serious	Not serious	Not serious	301/9380	13/10 000	24.68 (14.18 ; 42.98)	30.8 (17.1 ; 54.6)	Moderate	Important

[a] Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risk might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group).

[b] $I^2 = 0\%$.

[c] Few events and wide CI.

TB disease in household contacts irrespective of TB infection status compared with general population in high TB incidence countries (24 months)

Cumulative prevalence of active TB in household contacts irrespective of baseline TBI status in high TB incidence countries
Comparison with the general population (follow-up of 24 months)[a]

Quality assessment						No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population	RR (95% CI)	Absolute risk per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
5 *(8,15,16, 18,27)*	Cohort	Serious[b]	Not serious[c]	Not serious	Serious[d]	2/31	55/10 000	14.8 (9.82 ; 22.3)	83.9 (53.6 ; 129.5)	Low	Important
						37/335	100/10 000				
						9/108	82/10 000				
						55/508	41/10 000				
						73/1791	26/10 000				
Comparison: Household contacts aged 5–9 years vs general population											
1 *(8)*	Cohort	Serious[b]	Not serious	Not serious	Serious[d]	35/1464	26/10 000	9.2 (5.55 ; 15.23)	21.3 (11.8 ; 37)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(8)*	Cohort	Serious[b]	Not serious	Not serious	Serious[d]	45/1340	26/10 000	12.92 (8.0 ; 20.86)	31 (18.2 ; 51.6)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
5 *(8,15,16, 18,27)*	Cohort	Serious[b]	Serious[e]	Not serious	Not serious	8/102	55/10 000	6.29 (2.88 ; 13.72)	32.2 (11.4 ; 77.4)	Low	Important
						5/439	100/10 000				
						16/161	82/10 000				
						10/691	41/10 000				
						80/2804	26/10 000				
Comparison: Household contacts aged over 15 years vs general population											
3 *(8,16,27)*	Cohort	Serious[b]	Not serious[f]	Not serious	Not serious	34/432	100/10000	11.67 (7.55 ; 18.02)	59.4 (36.5 ; 94.7)	Moderate	Important
						49/719	41/10000				
						301/9380	26/10000				

[a] These comparisons are based on studies with a maximum follow-up of 24 months; therefore, TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring during 24 months.
[b] Ascertainment bias highly likely, as TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group). TB incidence in the population was estimated by multiplying the yearly notification rate by a factor of 2.
[c] Moderate heterogeneity among studies (I^2 = 67.1%) probably due to differences in background TB incidence.
[d] Few events and wide CI.
[e] High heterogeneity among studies (I^2 = 87.5%) probably due to differences in background TB incidence.
[f] Moderate heterogeneity among studies (I^2 = 72.5%) probably due to differences in background TB incidence.

PICO 2: What is the accuracy of WHO symptomatic screening to exclude TB disease in individuals with HIV on antiretroviral treatment (ART)?

Four-symptom screening plus chest radiographic findings to exclude TB disease in individuals with HIV

Population: Adults and adolescents with HIV on ART

Sensitivity	0.85 (95% CI: 0.70 ; 0.93)				
Specificity	0.30 (95% CI: 0.26 ; 0.33)	Prevalence	1%	5%	10%

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability, 1%	Pre-test probability, 5%	Pre-test probability, 10%	
True positives (patients with active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Serious[a]	None[b]	8 (7–9)	42 (35–46)	85 (70–93)	Moderate
False negatives (patients incorrectly classified as not having active TB)								2 (1–3)	8 (4–15)	15 (7–30)	
True negatives (patients without active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None[b]	295 (260–327)	283 (250–314)	268 (237–297)	High
False positives (patients incorrectly classified as having active TB)								695 (663–730)	667 (636–700)	632 (603–663)	

From references *(29,30)*

[a] Imprecise estimate for sensitivity. Downgraded by one.

[b] The possibility of publication bias is not excluded, but it was not considered of sufficient concern to downgrade.

PICO 3: What is the accuracy of symptomatic screening and/or chest x-ray to exclude TB disease in contacts of people with pulmonary TB without HIV in high TB incidence countries?

Chest radiographic findings for exclusion of TB disease in contacts of people with TB without HIV in high TB incidence countries

Index test: Chest X-ray. Any abnormality | Reference test: Sputum culture and/or smear
Place of testing: Triage
Test–treatment pathway: Chest X-ray positive → confirmatory test (mycobacterial culture or GeneXpert) → anti-TB chemotherapy (6–9 months' antibiotics)

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 10 000 Sensitivity: 0.94 (95% CI: 0.86 ; 0.98) Specificity: 0.87 (95% CI: 0.80 ; 0.92)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	7 studies 251 410 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%): 1882 (1716 ; 1954) Prevalence (5%): 4705 (4290 ; 4885	Moderate
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%) : 118 (46 ; 284) Prevalence (5%): 295 (115 ; 710)	
True negatives (patients without active TB)	7 studies 251 410 patients	Cross-sectional (cohort type accuracy study)	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%) : 85 064 (78 106 ; 89 866) Prevalence (5%): 82 460 (75 715 ; 87 115)	Moderate
False positives (patients incorrectly classified as having active TB)								Prevalence (2%) : 12 936 (8134 ; 19 894) Prevalence (5%): 12 540 (7 885 ; 19 285)	

From references *(31–37)*

[a] Limitations in study design (see QUADAS-2): High risk of selection bias in one study *(31)*. In all studies, less than half of participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture and/or smear negative (no active TB).
[b] Indirectness (see QUADAS-2): Some concern about applicability of reference standard in 2 studies – no downgrading.
[c] Inconsistency: Little heterogeneity for sensitivity and specificity (based on visual inspection of CIs).
[d] Imprecision: Precise estimates for sensitivity and specificity.
[e] Publication bias: Not applicable (the evidence base for publication bias in studies of diagnostic test accuracy is very limited).

Any symptom for exclusion of TB disease in contacts of people with TB without HIV in high TB incidence countries

Index text: Any symptom | Reference test: Sputum culture and/or smear
Place of testing: Triage
Test–treatment pathway: Symptom positive → confirmatory test (mycobacterial culture or GeneXpert) → anti-TB chemotherapy (6–9 months' antibiotics)

Outcome	Nos of studies and patients	Study design	Factors that may decrease quality of evidence					Effect per 10 000 Sensitivity: 0.73 (95% CI: 0.64 ; 0.80) Specificity: 0.77 (95% CI: 0.61 ; 0.87)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	11 studies 357 609 patients	Cross-sectional (cohort type accuracy study)	Very serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%): 1460 (1282 ; 1608) Prevalence (5%): 3650 (3205 ; 4020)	Low
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%): 540 (392 ; 718) Prevalence (5%):1350 (980 ; 1795)	
True negatives (patients without active TB)	11 studies 357 609 patients	Cross-sectional (cohort type accuracy study)	Very serious[a]	Not serious[b]	Serious[c]	Serious[d]	None[e]	Prevalence (2%):74 970 (60 074 ; 85 260) Prevalence (5%):72 675 (58 235 ; 82 650)	Very low
False positives (patients incorrectly classified as having active TB)								Prevalence (2%):23 030 (12 740 ; 37 926) Prevalence (5%):22 325 (12 350 ; 36 765)	

From references *(31–34,36,38–43)*

[a] Limitations in study design (see QUADAS-2): high risk of selection bias in 1 study (den Boon, 2006) and in two studies unclear risk of bias for the reference standard. In 9 of the 11 studies less than half the participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture and/or smear negative (no active TB) .

[b] Indirectness (see QUADAS-2): No major concern about applicability.

[c] Inconsistency: Moderate heterogeneity for sensitivity and significant heterogeneity for specificity (based on visual inspection of CIs) – downgrading on specificity.

[d] Imprecision: Precise estimates for sensitivity and imprecise estimate for specificity.

[e] Publication bias: Not applicable (the evidence base for assessing publication bias in studies of diagnostic test accuracy is very limited.

PICO 4: Could interferon-γ release assays be used as an alternative to tuberculin skin tests to identify individuals at greatest risk of progression from TB infection to TB disease in high TB incidence settings?

TST or IGRA for identifying individuals at greatest risk of progression to TB disease

Head-to head-evaluations of TST and IGRA (N = 5)
Review question: Among people at high risk of TBI who are not treated with TB preventive therapy, which test (e.g. TST or IGRA), when positive, can best identify individuals most at risk of progression?
Outcome: Predictive utility of the TST vs commercial IGRAs for progression to active TB
Patients/population: Longitudinal studies of adults and children without active TB at baseline not treated with preventive therapy
Setting: Community cohorts, individuals attending outpatient clinics (e.g. people living with HIV), individuals participating in RCTs, household contacts; all in high-incidence countries
Index test: TST (RT23 purified protein derivative or purified protein derivative S) and/or commercial blood-based IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB)
Importance: Longitudinal studies on the predictive value of a positive IGRA are still emerging in TB high-incidence countries (≥ 100/100 000). It is important to assess whether IGRA can be used as a replacement for the widely used TST.
Reference standard: All diagnoses of incident active TB (microbiologically confirmed or not)
Studies: Any longitudinal study design (e.g. prospective or retrospective cohort), in TB high-incidence countries, regardless of immunological status (e.g. HIV-infected or not) or BCG status. Average follow-up should be ≥ 1 year, but can be either active or passive.

Nos of studies and patients	Design	Quality				Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect	(GRADE)	
A. Systematic review outcome: Progression to active TB in untreated individuals									
5 (N = 7675 for TST, N = 7641 for IGRA) *(44–48)*	Prospectively followed cohorts	Serious (A1) (-1)	Serious TST: I^2 = 64.4% IGRA: I^2 = 49.6% (A2) (-1)	Not serious (A3)	TST: Serious imprecision IGRA: No serious imprecision (A4) (-1)	TST: RR = 1.49 (95% CI 0.79 ; 2.80) I^2 = 64.4% IGRA RR = 2.03 (95% CI 1.18 ; 3.50) I^2 = 49.6%	TST 10 more per 1000 (4 fewer to 37 more) IGRA 15 more per 1000 (3–36 more)	Very low	Critical
B. Systematic review outcome (sub-group analysis): Progression to active TB in immunocompromised people (HIV and other immunosuppressive conditions)									
2 (N = 725 for TST, N = 710 for IGRA) *(44, 45)*	Prospectively followed cohort of HIV-infected women before and after ART Prospectively followed cohort of HIV-infected individuals	Serious (B1) (-1)	Serious TST: I^2 = 77.4% IGRA: I^2 = 78.7% (B2) (-1)	Serious (B3) (-1)	Very serious (B4) (-2)	TST: RR = 1.64 (95% CI 0.24 ; 11.18) IGRA RR = 4.07 (95% CI 0.18 ; 92.72)	TST 39 more per 1000 (46 fewer to 616 more) IGRA 149 more per 1000 (40 fewer to 4438 more)	Very low	Critical

Nos of studies and patients	Design	Quality				Effect		Quality (GRADE)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect		
C. Systematic review outcome (sub-group analysis): Progression to active TB among contacts of TB cases									
1 (N = 1511 for TST, N = 1498 for IGRA) *(48)*	Prospective follow-up	Serious (C1) (-1)	Not assessed; single study (C2)	Serious C3 (-1)	Serious C4 (-1)	TST RR, single study = 1.31 (95% CI: 0.85 ; 2.04) IGRA RR, single study = 1.87 (95% CI: 1.12 ; 3.11)	TST 14 more per 1000 (7 fewer to 45 more) IGRA 28 more per 1000 (4 to 69 more)	Very low	Critical
D. Systematic review outcome (sub-group analysis): Progression to active TB among TB health-care workers									
1 (N = 195 for TST, N = 189 for IGRA) *(47)*	Prospective follow-up	Serious risk of bias (D1) (-1)	Not assessed; single study. (D2)	Serious D3 (-1)	Very serious D4 (-2)	TST RR, single study = 0.40 (95% CI: 0.02 ; 9.81) IGRA RR, single study = 3.10 (95% CI: 0.13 ; 75.04)	TST 6 fewer per 1000 (9 fewer to 82 more) IGRA (A difference cannot be computed)	Very low	Critical
E. Systematic review outcome (sub-group analysis): Progression to active TB among adolescents in a high-incidence setting									
1 (N = 5244 for both tests) *(46)*	Prospective follow-up	Serious (E1) (-1)	Not assessed; single study (E2)	Serious E3 (-1)	No serious E4	TST RR, single study = 2.71 (95% CI: 1.42 ; 5.15) IGRA RR, single study = 2.89 (95% CI: 1.55 ; 5.41)	TST 9 more per 1000 (2 to 21 more) IGRA 10 more per 1000 (3 to 22 more)	Very low	Critical

Notes on GRADE summary table

Overall quality:
All studies start with one point taken off because none were RCTs. The lowest quality score achievable is 1 out of 4; no minus scores are given.
Quality assessment: Based on the relative effect measure (RR or IRR) for both TST and IGRA. Studies not marked down if estimates for both tests score high on a specific GRADE quality item.

Other study quality considerations: Newcastle-Ottawa Scale quality items were considered when assessing the risk of bias. One point is docked if at least one concern is present.
A1: Risk of bias is possible. Issues in the studies include selection bias, risk of incorporation bias, ascertainment and publication bias. Methods for ascertaining TB included microbiological methods, but not all incident TB cases had a definite culture-confirmed diagnosis of TB. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or unpublished; their results were not included in this analysis; however, addition of their results is not expected to change the overall conclusions of this review.
A2: Serious unexplained inconsistency of RR estimate for TST. Points taken off if serious inconsistency identified in either estimate.
A3: Although the number of studies included is small, they involve a range of populations, including adults and children, immunocompromised people and TB contacts, providing direct evidence for these groups.
A4: Serious imprecision of RR estimate for TST. Lower limit of 95% CI indicates lack of predictive utility. Points docked if serious imprecision identified in either estimate.

B1: Risk of bias is possible. Issues include selection bias, risk of incorporation bias, ascertainment and publication bias. Incorporation bias could not be ruled out in the cohort that included antepartum and postpartum women because information was not available; moreover, there is concern about selection. The ART cohort study reported reference standards that do not account for index tests; however, assessors were not blinded to baseline TST results that were recorded in patient records. Methods for ascertaining TB included microbiological methods, but not all incident TB cases had a definitive diagnosis of TB. Publication bias not formally assessed but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis; however, addition of results is not expected to change the overall conclusions of this review.
B2: Serious unexplained inconsistency in RR estimates for both TST and IGRA.
B3: This pooled estimate is based on only two studies: one study of HIV-infected people on ART with a median CD4+ approximately 250, and one on HIV-infected antepartum and postpartum women. No direct evidence for treatment-naïve patients and/or HIV-infected patients with high CD4 counts or other sub-populations of HIV-infected individuals (e.g. children).
B4: Very serious imprecision of RR estimates for both TST and IGRA. CIs are wide and indicate both significant predictive performance and lack of predictive utility. Studies had few events.

C1: Risk of bias is possible. Issues include selection bias, risk of incorporation bias (no information) and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis; however, addition of results is not expected to change the overall conclusions of this review.
C2: Inconsistency not assessed.
C3: This single study comprises household case contacts in a high-incidence country. No direct evidence for other subpopulations of case contacts.
C4: Serious imprecision of TST effect estimates. Lower limit of 95% CI indicates lack of predictive utility.

D1: Risk of bias is possible. Issues include selection bias, lack of use of microbiological tools in methods to ascertain TB, incorporation bias and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis; however, addition of results is not expected to change the overall conclusions of this review.
D2: Inconsistency not assessed.
D3: This single study comprises health-care workers at a primary health care clinic. No direct evidence for other subpopulations of health-care workers or all settings of health care.
D4: Very serious imprecision of IGRA and TST effect estimates; CIs are wide and indicate both significant predictive performance and lack of predictive utility.

E1: Risk of bias is possible. Issues include selection bias, incorporation of index tests in methods to ascertain incident TB and publication bias. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and/or are unpublished; their results were not included in this analysis; however, addition of results is not expected to change the overall conclusions of this review.
E2: Inconsistency not assessed.
E3: This single study comprises adolescents in a high-incidence setting. No direct evidence for other subpopulations of children or adolescents.
E4: No serious imprecision: Few events with large sample size.

PICO 5: Should 3-month daily rifampicin plus isoniazid (3RH) be offered as a preventive treatment option for children and adolescents <15 years of age as an alternative to 6 or 9 months' isoniazid (INH) monotherapy in high TB incidence countries?

3-month daily rifampicin and isoniazid in children and adolescents < 15 years

Overall quality: low

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin and isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
"Radiological" TB disease: follow up: range 3–7 years to 7–11 years; assessed with: chest radiography												
1 *(49)*	Randomized trial	Serious[a]	Not serious	Serious[b]	Not serious	None	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318 ; 0.762)	122 fewer per 1000 (from 57 to 164 fewer)	Low	Critical
Mortality												
0									Cannot be estimated		–	Important
Adverse events: follow up: range 3–7 years to 7–11 years; assessed by: recognition of symptoms and elevated liver enzymes												
1 *(49)*	Randomized trial	Very serious[a,c]	Not serious	Serious[d]	Not serious	None	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197 ; 0.559)	83 fewer per 1000 (from 55 to 100 fewer)	Very low	Critical
Adverse events: follow up: median 97–197 days; assessed by: liver toxicity test and clinical												
1 *(50)*	Observational study	Serious[e]	Not serious	Serious[d]	Serious[f]	None	1/220 (0.5%)	5/264 (1.9%)	RR 0.24 (0.03 ; 2.04)	14 fewer per 1000 (from 18 fewer to 20 more)	Very low	Critical
Completion rate: follow up: range 3–7 years to 7–11 years[#]												
1 *(49)*	Randomized trial	Serious[g]	Not serious	Serious[d]	Not serious	None	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01 ; 1.14)	60 more per 1000 (from 9 to 121 more)	Low	Critical
Completion rate: assessed by: completion of > 80% of treatment without interruption of > 2 months												
1 *(51)*	Observational study	Serious[e]	Not serious	Not serious	Serious[h]	None	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70 ; 3.43)	389 more per 1000 (from 193 to 671 more)	Very low	Critical

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin and isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
Drug-resistant TB												
0									Cannot be estimated		–	Important

From references *(49–51)*

[a] Although there was a risk of selection bias, the characteristics of the two groups were similar. Patients with poor compliance were not included in the analysis of treatment outcomes. Downgraded by one level.

[b] There was no clinical disease. The outcome reported was new radiographic findings suggesting possible active disease. No data compared with 6H. Downgraded by one level.

[c] A high risk of detection bias due to lack of blinding. The RH group included participants enrolled during the second period, whose characteristics were different; they were not randomized between the RH group and the 9H group. Downgraded by two levels.

[d] No data compared with 6H. Downgraded by one level.

[e] Risk of bias due to poor comparability of the two groups. Downgraded by one level.

[f] Low event rate and wide 95% CI. Downgraded by one level.

[g] Lack of blinding. Medication adherence test was performed at home by parents. Although there was a risk of selection bias, the characteristics of the two groups were similar. Downgraded by one level.

[h] Wide 95% CI. Downgraded by one level.

The study reported adherence rates; compliance was considered to be poor if no medication was detected in urine strips or if patients did not return for follow-up visits or were lost to follow-up. Poor compliance was considered non-completion in the analysis.

PICO 6: In people of all ages at risk of TB disease, does a 4-month daily rifampicin regimen safely prevent TB disease as compared with other recommended TB preventive treatment regimens?

Overall quality: moderate
Bibliography: (see references *52–56*)

Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. New Eng J Med. 2018 Aug 2;379(5):440–53.
Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah, J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379:454–463.
Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2008;149(10):689–697.
Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med. 2004;170(4):445–449.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with 4 months of daily rifampicin	a regimen of 9 months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Incidence of active TB (in all forms) in adults (follow up: mean 28 months; assessed with: RCT evidence)												
1 [a]	randomized trials [b,c]	serious [d,e]	not serious	not serious [f]	not serious	none	8/3443 [g]	9/3416 [g]	Rate ratio 0.88 (0.34 to 2.28) [h]	0 fewer per 1000 patient(s) per years (from 2 fewer to 2 more) [i,j]	Moderate	Critical
Incidence of active TB (microbiologically confirmed) in adults (follow up: mean 28 months; assessed with: RCT evidence)												
1 [a]	randomized trials [b,c]	serious [d,e]	not serious	not serious [f]	not serious	none	4/3443 [g]	4/3416 [g]	Rate ratio 0.99 (0.25 to 3.96) [h]	0 fewer per 1000 patient(s) per years (from 1 fewer to 2 more) [i,j]	Moderate	Critical
Mortality (all cause) in adults during treatment (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	0/3280 (0.0%) [k]	4/3205 (0.1%) [k,l]	RR 0.11 (0.01 to 2.02) [h,m]	1 fewer per 1000 (from 3 to 0 fewer) [n]	Moderate	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Mortality (related to drug) in adults during treatment (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	0/3280 (0.0%) [k]	1/3205 (0.0%) [k,l]	RR 0.33 (0.01 to 8.00) [h,m]	0 fewer per 1000 (from 1 to 0 fewer) [n]	Moderate	Critical
Adverse events (grades 3-5) in adults (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	53/3280 (1.6%) [k,o]	119/3205 (3.7%) [k,o]	RR 0.44 (0.32 to 0.60) [h]	21 fewer per 1000 (from 25 to 15 fewer)	Moderate	Critical
Adverse events (related grades 3-5) in adults (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	not serious	none	31/3280 (0.9%) [k,o]	75/3205 (2.3%) [k,o]	RR 0.40 (0.27 to 0.61) [h]	14 fewer per 1000 (from 20 to 8 fewer) [n]	Moderate	Critical
Treatment completion (ever) in adults (assessed with: RCT evidence)												
3	randomized trials [b,p]	serious [q]	not serious	not serious [f]	not serious	none	2763/3501 (78.9%) [r]	2188/3474 (63.0%) [r]	RR 1.25 (1.22 to 1.29) [h]	157 more per 1000 (from 139 to 183 more)	Moderate	Important
Incidence of active TB (in all forms) in paediatrics (follow up: mean 16 months; assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [u,v]	not serious	not serious [f]	not serious	none	0/422	2/407	Rate ratio 0.19 (0.01 to 4.02) [h,w]	4 fewer per 1000 patient(s) per years (from 9 fewer to 1 more) [i,x]	Moderate	Critical
Incidence of active TB (microbiologically confirmed) in paediatrics (follow up: mean 16 months; assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [u,v]	not serious	not serious [f]	not serious	none	0/422	2/407	Rate ratio 0.19 (0.01 to 4.02) [h,w]	4 fewer per 1000 patient(s) per years (from 9 fewer to 1 more) [i,j]	Moderate	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Mortality (all cause) in paediatrics during treatment (assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	1/422 (0.2%)	0/407 (0.0%)	RR 2.89 (0.12 to 70.82) [h,m]	2 more per 1000 (from 2 fewer to 7 more) [n,y]	Moderate	Critical
Mortality (related to drug) in paediatrics during treatment (assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	0/422 (0.0%)	0/407 (0.0%)	RR 0.96 (0.02 to 48.50) [h,m]	0 fewer per 1000 (from 1 fewer to 1 more) [n,y]	Moderate	Critical
Adverse events (grades 3-5) in paediatrics (assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	1/422 (0.2%)	1/407 (0.2%)	RR 0.96 (0.06 to 15.37) [h]	0 fewer per 1000 (from 6 fewer to 7 more) [n,y]	Moderate	Critical
Adverse events (related grades 3-5) in paediatrics (assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [v]	not serious	not serious [f]	not serious	none	0/422 (0.0%)	0/407 (0.0%)	RR 0.96 (0.02 to 48.50) [h,m]	0 fewer per 1000 (from 1 fewer to 1 more) [n,y]	Moderate	Critical
Treatment completion (ever) in paediatrics (assessed with: RCT evidence)												
1	randomized trials [s,t]	serious [q]	not serious	not serious [f]	not serious	none	365/422 (86.5%)	314/407 (77.1%)	RR 1.12 (1.05 to 1.20) [h]	136 more per 1000 (from 79 to 193 more) [n,z]	Moderate	Important
Incidence of active TB (microbiologically confirmed) in HIV-positive adults (follow up: mean 28 months; assessed with: RCT evidence)												
1 [a]	randomized trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/132 [ab,g]	0/138 [ab]	Rate ratio 2.88 (0.12 to 70.67) [h,w]	8 more per 1000 patient(s) per years (from 7 fewer to 22 more) [ac]	Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a regimen with four months of daily rifampicin	a regimen of nine months of daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Incidence of active TB (in all forms) in HIV-positive adults (follow up: mean 28 months; assessed with: RCT evidence)												
1 [a]	randomized trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/132 [ab,g]	2/138 [ab,g]	Rate ratio 0.48 (0.04 to 5.29) [h]	7 fewer per 1000 patient(s) per years (from 32 fewer to 18 more) [ac]	Low	Critical
Adverse events (grades 3-5) in HIV-positive adults (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	2/130 (1.5%) [ab,ad]	8/138 (5.8%) [ab,ad]	RR 0.27 (0.06 to 1.23) [h]	43 fewer per 1000 (from 87 fewer to 2 more) [ac]	Low	Critical
Adverse events (related grades 3-5) in HIV-positive adults (assessed with: RCT evidence)												
2	randomized trials [b,c]	serious [d]	not serious	not serious [f]	serious [aa]	none	1/130 (0.8%) [ab,ad]	5/138 (3.6%) [ab,ad]	RR 0.21 (0.03 to 1.79) [h]	29 fewer per 1000 (from 63 fewer to 6 more) [ac]	Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

[a] The GDG decided that for efficacy outcomes the pooled outcomes for phase 2 and phase 3 studies be considered one trial as the same protocol was used for both phases conducted by the same investigating team, even if the number of sites increased in the phase 3 study. Although the quality was not downgraded for this, the GDG noted that Inconsistency could not be judged given that there was only a single trial. Ideally replication by other trials would be desirable. For adverse events the studies can be considered as two separate trials.

[b] Phase 2 *(54)* and Phase 3 *(52)* open-label trials conducted in nine countries, assigning adults with latent tuberculosis infection to receive treatment with a 4-month regimen of daily rifampicin or a 9-month regimen of daily isoniazid. The primary outcome in the phase 2 trial was incidence of grade 3 to 5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active tuberculosis within 28 months of randomization. The primary outcome of the phase 3 trial was microbiologically confirmed active tuberculosis within 28 months after randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active tuberculosis, grade 3 to 5 adverse events, and treatment completion. Outcomes of active tuberculosis and adverse events were adjudicated by three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits.

[c] Between the phase 2 and phase 3 trials in adults, there were no significant changes in guidelines or risk profiling of latent TB reactivation in terms of judging 'increased risk for reactivation'. Randomization in both trials was stratified by site and centrally computer-randomized. Patients were randomized 1:1 in blocks of varying length (2 to 8) to isoniazid or rifampicin.

[d] Open label design but endpoints of active TB and adverse events adjudicated by three-member, independent, blinded review panels. There were 18 per protocol exclusions among those randomized to isoniazid and 19 per protocol exclusions among those randomized to rifampicin. These per protocol exclusions were due to being a household contact of a tuberculosis patient with resistance to isoniazid or rifampicin (proven post-randomization). There were nine individuals randomized to isoniazid and five individuals randomized to rifampicin who withdrew consent after randomization. The GDG decided to downgrade by one level because of the open label design possibly led to performance bias.

[e] Among those randomized to isoniazid and forming the modified intention-to-treat population, 260 individuals were lost to follow-up. Among those randomized to rifampicin and forming the modified intention-to-treat population, 245 individuals were lost to follow-up. In the modified intention-to-treat population, 7.4% of individuals were lost to follow-up.

[f] The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 4R with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TPT. Some study sites were low TB incidence settings for which a WHO recommendation for use of 4R already exists.

[g] All active TB events occurred within the phase 3 trial *(52)*.

[h] Unadjusted estimate.

[i] The rate difference was estimated by a Poisson model with the use of generalized estimating equations with a log link and the inclusion of the log of person-time as an offset. An exchangeable correlation structure with robust standard errors was used to account for the correlation of participants coming from the same household.

[j] Values reported as per Table 3 of *(52)*. Values include Phase 2 results *(54)* as well.

[k] Denominators are representative of the combined safety population of phase 2 *(54)* and phase 3 *(52)* as indicated in supplemental tables S2 and S3 of the phase 3 publication. From the phase 2 trial, 396 patients receiving isoniazid and 393 patients receiving rifampicin formed the safety population; from the phase 3 trial, 2809 patients receiving isoniazid and 2887 patients receiving rifampicin formed the safety population.

[l] All mortality events occurred in the phase 3 trial *(52)*.

[m] A zero cell correction of 0.5 has been used to calculate the risk ratio.

[n] The risk difference was estimated by a binomial distribution model with an identity link and generalized estimating equations. An exchangeable correlation structure and robust standard errors were used to account for correlation of patients coming from the same family. If no events occurred in one or both arms, confidence intervals were calculated based on *(56)*.

[o] Among adverse events from the phase 2 trial *(54)*, 10 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 7 were deemed possibly/probably related to study drug; 19 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 16 were deemed possibly/probably related to study drug. Among adverse events from the phase 3 trial *(52)*, 43 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 24 were deemed possibly/probably related to study drug; 100 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 59 were deemed possibly/probably related to study drug.

[p] Also included is the phase 1 trial *(55)*, a single centre, open-label randomized trial assessing superiority of 4 months of daily rifampicin to 9 months of daily isoniazid for treatment completion.

[q] Open label trial, unblinded assessment of compliance judged on the basis of pill counts at monthly follow-up visits.

[r] Numerator and denominator values are derived from the Phase 1 trial *(55)*, Phase 2 trial *(54)*, and Phase 3 trial *(52)*. Treatment completion was defined as taking at least 80% of prescribed doses (i.e., at least 96 pills of rifampicin or 216 pills of isoniazid). In the phase 1 trial, 44 of 58 individuals randomized to isoniazid and 53 of 58 individuals randomized to rifampicin completed treatment. In the phase 2 trial, 254 of 427 individuals randomized to isoniazid and 328 of 420 individuals randomized to rifampicin completed treatment. In the phase 3 trial, 1890 of 2989 individuals randomized to isoniazid and 2382 of 3023 individuals randomized to rifampicin completed treatment.

[s] Open-label, non-inferiority trial conducted in seven countries, assigning children with latent tuberculosis infection to receive treatment with a 4-month regimen of rifampicin or a 9-month regimen of isoniazid for the incidence of grade 3 to 5 adverse events during treatment. Secondary outcomes were the incidence of microbiologically confirmed active tuberculosis within 16 months after randomization and completion of the treatment regimen. Outcomes of active TB and adverse events were adjudicated by two- or three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits *(53)*.

[t] Randomization in the paediatric trial was stratified by country and centrally computer-randomized. Patients were randomized 1:1 in blocks of varying length (2 to 8) to isoniazid or rifampicin. Enrollment and randomization in this trial was completely separate from the adult trials.

[u] Among those randomized to isoniazid and forming the modified intention-to-treat population, there were 6 individuals lost to follow-up. Among those randomized to rifampicin and forming the modified intention-to-treat population, there were 5 individuals lost to follow-up. Among all children forming the modified intention-to-treat population, 1.3% of individuals were lost to follow-up.

[v] Open label design but endpoints of active TB and adverse events adjudicated by two-member and three-member, respectively, independent, blinded review panels. There were 9 per protocol exclusions among those randomized to isoniazid and 6 per protocol exclusions among those randomized to rifampicin. These per protocol exclusions were due to being tuberculin skin test negative at the end of the window period (two months after exposure). GDG decided to downgrade by one level because of the open label design and because some sites were not high burden.

[w] A zero cell correction of 0.5 has been used to calculate the rate ratio.

[x] Values as reported in the text of the paediatric trial *(53)*.

[y] Values as reported in Table 3 of the paediatric trial *(53)*.

[z] Values reported in Table 2 of the paediatric trial *(53)*.

[aa] Subgroup analysis within randomized trials that involved relatively small numbers of HIV-infected patients when compared to all patients included in the trials.

[ab] Denominators include HIV-positive patients known at the time of randomization as reported in Supplemental Table S1 of the phase 3 adult trial *(52)*, as well as patients diagnosed post randomization as a result of baseline assessment. This includes 130 patients and 8 patients receiving isoniazid with an HIV-diagnosis at time of randomization and post-randomization, respectively, and 125 patients and 7 patients receiving rifampicin with an HIV-diagnosis at time of randomization and post-randomization, respectively. This resulted in modified intention to treat population sizes of 132 for rifampicin and 138 for isoniazid. Among HIV-positive patients randomized to rifampicin, 2 did not receive a dose of therapy. Thus, the safety population sizes were 130 for rifampicin and 138 for isoniazid.

[ac] Unadjusted absolute estimate.

[ad] Among patients receiving rifampicin included in the safety population, 6 patients were HIV-positive in the phase 2 trial and 124 patients were HIV-positive in the phase 3 trial. All grade 3–5 adverse events among patients receiving rifampicin occurred in the phase 3 trial. Two patients experienced a grade 3–5 adverse event with rifampicin that resulted in permanent discontinuation of the study drug, only 1 was deemed possibly/probably related to the study drug. Among patients receiving isoniazid included in the safety population, 7 patients were HIV-positive in the phase 2 trial and 131 were HIV-positive in the phase 3 trial. One patient in the phase 2 trial and 7 patients in the phase 3 trial receiving isoniazid experienced a grade 3–5 adverse event resulting in permanent discontinuation of the study medication. The events were deemed possibly/probably related to the study drug for the one patient from the phase 2 trial and for 4 patients from the phase 3 trial.

PICO 7: In people of all ages at risk of TB disease, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease as compared with other recommended TB preventive treatment regimens?

Population: PLHIV at increased risk of active TB
Overall quality: low
Bibliography: (see reference 57)[a]

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month daily rifapentine plus isoniazid	9 months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Incidence of active TB (follow up: mean 3 years; assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored)												
1	randomized trials	serious[b,c]	not serious	serious[d]	not serious	none	29/1488 (1.9%)	26/1498 (1.7%)	Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)	–	Low	Critical
Incidence of active TB among ART-naive participants at entry (follow up: mean 3 years; assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored)												
1	randomized trials	serious[b,c]	not serious	serious[d]	not serious	none	17/740 (2.3%)	15/746 (2.0%)	Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)	–	Low	Critical
Incidence of active TB among TST or IGRA positive participants at entry (follow up: mean 3 years; assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored)												
1	randomized trials	serious[b,c]	not serious	serious[d]	not serious	none	9/337 (2.7%)	10/349 (2.9%)	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	–	Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month daily rifapentine plus isoniazid	9 months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Incidence of bacteriologically confirmed TB (follow up: mean 3 years; assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored)												
1	randomized trials	serious [c,e]	not serious	serious [d]	not serious	none	18/1488 (1.2%)	14/1498 (0.9%)	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	-	Low	Critical
Time to TB diagnosis or death related to TB, with other deaths treated as competing risk (follow up: mean 3 years; assessed with: RCT evidence (mITT population))												
1	randomized trials	serious [f]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	2 more per 1000 (from 6 fewer to 15 more)	Low	Critical
							-	1.7% g		2 more per 1000 (from 6 fewer to 15 more)		
Incidence of active TB or death due to unknown cause (follow up: mean 3 years; assessed with: RCT evidence (mITT population))h												
1	randomized trials	serious [i]	not serious	serious [d]	not serious	none	32/1488 (2.2%)	33/1498 (2.2%)	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	-	Low	Critical
Incidence of active TB or death due to unknown cause (follow up: mean 3 years; assessed with: RCT evidence (per-protocol population))												
1	randomized trials	serious [i]	not serious	serious [d]	not serious	none	31/1456 (2.1%)	29/1381 (2.1%)	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	-	Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month daily rifapentine plus isoniazid	9 months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Incidence of active TB or death from any cause (follow up: mean 3 years; assessed with: RCT evidence (mITT population))												
1	randomized trials	serious [c]	not serious	serious [d]	not serious	none	45/1488 (3.0%)	51/1498 (3.4%)	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	-	Low	Critical
Time to death from any cause (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c,i]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	5 fewer per 1000 (from 11 fewer to 6 more)	Low	Critical
							-	1.9% [g,j]		5 fewer per 1000 (from 11 fewer to 6 more)		
Time to death from TB (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	serious [d]	serious [k]	none	3/1488 (0.2%)	3/1498 (0.2%)	HR 1.00 (0.20 to 4.93)	0 fewer per 1000 (from 2 fewer to 8 more) l	Very low	Critical
Adverse events (grade 3 or higher of nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy) (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	serious [d]	not serious	none	44/1488 (3.0%)	52/1498 (3.5%)	RR 0.86 (0.58 to 1.27)	5 fewer per 1000 (from 15 fewer to 9 more)	Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month daily rifapentine plus isoniazid	9 months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	serious [d]	not serious	none	83/1488 (5.6%)	108/1498 (7.2%)	RR 0.79 (0.59 to 1.04)	15 fewer per 1000 (from 30 fewer to 3 more)	Low	Critical
Treatment completion (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c,m]	not serious	serious [d]	not serious	none	1444/1488 (97.0%)	1341/1498 (89.5%)	RR 1.04 (0.99 to 1.10)	36 more per 1000 (from 9 fewer to 90 more)	Low	Critical
Treatment completion among ART-naive participants at entry (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c,m]	not serious	serious [d]	not serious	none	720/740 (97.3%)	656/743 (88.3%)	RR 1.05 (0.97 to 1.14)	44 more per 1000 (from 26 fewer to 124 more)	Low	Critical
Emergence of drug resistance to isoniazid among those with confirmed TB and with DST (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	2/14 (14.3%)	1/12 (8.3%)	RR 1.63 (0.17 to 15.99)	52 more per 1000 (from 69 fewer to 1000 more)	Very low	Important
Emergence of drug resistance to rifampicin among those with confirmed TB and with DST (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	1/15 (6.7%)	1/12 (8.3%)	RR 0.81 (0.06 to 11.77)	16 fewer per 1000 (from 78 fewer to 898 more)	Very low	Important
Emergence of drug resistance to ethambutol among those with confirmed TB and with DST												
1	randomized trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/7 (0.0%)	1/7 (14.3%)	not estimable		Very low	Important

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 month daily rifapentine plus isoniazid	9 months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
Emergence of drug resistance to pyrazinamide among those with confirmed TB and with DST (follow up: mean 3 years; assessed with: RCT evidence)												
1	randomized trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		Very low	Important

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

[a] Randomized, open-label, phase 3 noninferiority trial comparing the efficacy and safety of a 1-month regimen of daily rifapentine plus isoniazid (1-month group) with 9 months of isoniazid alone (9-month group) in HIV-infected patients who were living in areas of high TB prevalence or who had evidence of latent TB infection. Primary end point was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. TBI was not confirmed in about 80% of participants. Enrolment restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Overall TB incidence observed in the trial was lower than expected. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority nor noninferiority of the 1-month regimen was shown in this stratum.

[b] Unknown cause of death censored in this analysis, which may cause bias in incidence rate difference if some of these deaths were related to TB (dependent censoring)

[c] The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 1HP with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TPT. The GDG noted that Inconsistency could not be judged given that there was only a single trial; results from more trials would be desirable.

[d] Trial conducted only in PLHIV and not in all people at risk of active TB.

[e] Probable TB diagnoses and deaths with non-bacteriologically confirmed TB censored at the time of event

[f] When cause of death was determined to be unknown or not related to TB by blinded external reviewers, these were treated as a competing risk rather than endpoint. Some of these may have actually been due to TB, which may bias estimate.

[g] The proportion of events among controls

[h] Per-protocol population consisted of all participants who completed treatment, or who had died or received a TB diagnosis while they were receiving treatment.

[i] Deaths were reviewed by blinded external reviewers. Unknown causes of death were included as an endpoint, but misclassification of cause of death may bias estimate

[j] There were 21 deaths in the 1-month arm, 3 related to TB. There were 28 deaths in the 9-month arm, 3 related to TB.

[k] Small number of events

[l] Incidence rate difference per 100 person-years of 0.00 (-0.10 to 0.10)

[m] Assessed via participant self-report at clinic visits

[n] Resistance may be non-emergent and coming from infecting strain

[o] Small sample of bacteriologically confirmed TB who had drug susceptibility test results

PICO 8: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of TB infection in high TB incidence countries?

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for TBI treatment in adults with HIV

Population: Adults with HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: high

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months weekly rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
Active TB												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[a]	Serious[b]	None	26/534 (4.9%)	28/520 (5.4%)	RR 0.733 (0.234 ; 2.295)	14 fewer per 1000 (from 41 fewer to 70 more)	Moderate	Critical
All-cause mortality												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[a]	Serious[b]	None	23/535 (4.3%)	30/513 (5.8%)	RR 0.746 (0.438 ; 1.270)	15 fewer per 1000 (from 16 more to 33 fewer)	Moderate	Important
Any adverse events (grade III or IV)												
2 *(58,59)*	RCTs	Serious[c]	Not serious	Not serious[a]	Not serious	None	39/535 (7.3%)	59/513 (11.5%)	RR 0.627 (0.426 ; 0.921)	43 fewer per 1000 (from 9 to 66 fewer)	Moderate	Critical
Hepatotoxicity												
2 *(58,59)*	RCTs	Not serious[d]	Not serious	Not serious[a]	Not serious	None	8/535 (1.5%)	30/513 (5.8%)	RR 0.256 (0.118 ; 0.553)	44 fewer per 1000 (from 26 to 52 fewer)	High	Critical
Drug resistant TB												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[a]	Very serious[e]	None	3/534 (0.6%)	1/520 (0.2%)	RR 2.001 (0.259 ; 15.436)	2 more per 1000 (from 1 fewer to 28 more)	Low	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months weekly rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
Completion rate												
2 *(58,59)*	RCTs	Not serious	Not serious	Not serious[a]	Not serious	None	497/534 (93.1%)	397/520 (76.3%)	RR 1.255 (1.014 ; 1.553)	195 more per 1000 (from 11 to 422 more)	High	Critical

[a] Although one of the trials was conducted in low TB incidence countries, this is unlikely to affect the relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Not downgraded.
[b] 95% CIs of both relative and absolute effect include appreciable benefit and harm with 3HP.
[c] Both trials were open-label, which may have introduced bias in ascertainment of adverse events.
[d] Although the trials were open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests.). Not downgraded.
[e] Very low event rates. Upper limit of 95% CI of both relative and absolute effect include appreciable harm with 3HP. Downgraded by two levels.

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of TB infection in adults without HIV

Population: Adults without HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
Active TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[a]	Not serious[b]	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179 ; 1.074)	2 fewer per 1000 (from 0 to 3 fewer)	Moderate	Critical
All-cause mortality												
1 *(60)*	RCT	Not serious	Not serious	Serious[a]	Not serious[c]	None	31/3986 (0.8%)	39/3759 (1.0%)	RR 0.740 (0.462 ; 1.183)	3 fewer per 1000 (from 2 more to 6 fewer)	Moderate	Important
Any adverse events (grade III or IV)												
1 *(60)*	RCT	Serious[d]	Not serious	Serious[a]	Not serious	None	229/4040 (5.7%)	244/3759 (6.5%)	RR 0.873 (0.733 ; 1.040)	8 fewer per 1000 (from 3 more to 17 fewer)	Low	Critical
Hepatotoxicity												
1 *(60)*	RCT	Not serious[e]	Not serious	Serious[a]	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099 ; 0.268)	23 fewer per 1000 (from 20 to 25 fewer)	Moderate	Critical
Drug-resistant TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[a]	Not serious[c]	None	1/3986 (0.0%)	2/3745 (0.1%)	RR 0.470 (0.043 ; 5.179)	0 fewer per 1000 (from 1 fewer to 2 more)	Moderate	Important
Completion rate												
1 *(60)*	RCT	Not serious	Not serious	Serious[a]	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159 ; 1.221)	131 more per 1000 (from 110 to 153 more)	Moderate	Critical

[a] No comparison with 6 months of isoniazid. The study included 2.7% HIV-positive participants. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[b] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[c] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[d] An open-label design of the trial may have introduced ascertainment bias.
[e] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of TB infection in children and adolescents

Population: Children and adolescents
Comparison: 6 or 9 months isoniazid
Overall quality: moderate

Quality assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Active TB												
1 *(61)*	RCT	Not serious	Not serious	Serious[a]	Not serious[b]	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007 ; 2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	Moderate	Critical
All-cause mortality												
1 *(61)*	RCT	Not serious	Not serious	Serious[a]	Not serious[c]	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009 ; 3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	Moderate	Important
Any adverse events (Grade III or IV)												
1 *(61)*	RCT	Serious[d]	Not serious	Serious[a]	Not serious[c]	None	7/539 (1.3%)	8/493 (1.6%)	RR 0.875 (0.320 ; 2.396)	2 fewer per 1000 (from 11 fewer to 23 more)	Low	Critical
Hepatotoxicity												
1 *(61)*	RCT	Not serious[e]	Not serious	Serious[a]	Not serious	None	0/539 (0.0%)	0/493 (0.0%)	Cannot be estimated	0 fewer per 1000 (from 4 fewer to 4 more)	Moderate	Critical
Drug-resistant TB												
0									Cannot be estimated		–	Important
Completion rate												
1 *(61)*	RCT	Not serious	Not serious	Serious[a]	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030 ; 1.153)	72 more per 1000 (from 24 to 124 more)	Moderate	Critical

[a] No comparison against 6 months of isoniazid. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[b] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[c] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[d] An open-label design of the trial may have introduced ascertainment bias.
[e] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

PICO 9: In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens?

Population: Isoniazid Preventive Therapy (IPT) compared to no IPT or placebo in pregnant women with HIV.
Bibliography:[a] (see references *62–65*)
Overall quality of evidence rating: low

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	no IPT or placebo	Relative (95% CI)	Absolute (95% CI)		
Composite pregnancy outcomes (low birth weight, preterm delivery spontaneous abortion, stillbirth, or congenital anomaly)												
1	randomized trials *(62)*	not serious	not serious	not serious	serious [a]	none	106/449 (23.6%)	78/460 (17.0%)	OR 1.51 (1.09 to 2.10)	66 more per 1000 (from 12 to 131 more)	Moderate	Critical
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, neonatal mortality, or congenital anomaly)												
2	observational studies *(64,65)*	very serious [b]	not serious	not serious	serious [a]	none	43/172 (25.0%)	63/175 (36.0%)	OR 0.471 (0.199 to 0.742)	151 fewer per 1000 (from 259 to 66 fewer)	Very low	Critical
Maternal death												
1	randomized trials *(62)*	not serious	not serious	not serious	very serious [c]	none	1/477 (0.2%)	3/479 (0.6%)	RR 0.33 (0.03 to 3.21)	4 fewer per 1000 (from 6 fewer to 14 more)	Low	Critical
Maternal death												
2	observational studies *(63,64)*	very serious [b]	not serious	not serious	not serious	none	18/10786 (0.2%)	105/41311 (0.3%)	RR 0.65 (0.39 to 1.07)	1 fewer per 1000 (from 2 to 0 fewer)	Low	Critical
Grade 3 or 4 adverse events related to study treatment												
1	randomized trials *(62)*	not serious	not serious	not serious	serious [a]	none	34/477 (7.1%)	22/479 (4.6%)	RR 1.55 (0.92 to 2.61)	25 more per 1000 (from 4 fewer to 74 more)	Moderate	Critical
Hepatotoxicity												
1	randomized trials *(62)*	not serious	not serious	not serious	serious [a,d]	none	18/477 (3.8%)	11/479 (2.3%)	RR 1.64 (0.78 to 3.44)	15 more per 1000 (from 5 fewer to 56 more)	Moderate	Critical
Hepatotoxicity												
1	observational studies *(63)*	very serious [e]	not serious	not serious	not serious [f]	none	30/17015 (0.2%)	114/41227 (0.3%)	RR 1.01 (0.68 to 1.51)	0 fewer per 1000 (from 1 fewer to 1 more)	Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	no IPT or placebo	Relative (95% CI)	Absolute (95% CI)		
Discontinuation of study drug due to toxicity												
1	randomized trials *(62)*	not serious	not serious	not serious	serious [d]	none	11/477 (2.3%)	8/479 (1.7%)	RR 1.38 (0.56 to 3.40)	6 more per 1000 (from 7 fewer to 40 more)	Moderate	Critical

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

[a] Optimal information size not met.
[b] Bias due to confounding is considered serious. Important confounders are not fully accounted for.
[c] Large CI including both appreciable benefits and harms and very few events d. CI includes both appreciable benefits and harms
[e] Confounding was not accounted for. Bias due to measurement of hepatotoxicity is considered serious since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT.
[f] Very large sample size and CI of absolute effect is very narrow.

Population: Immediate Isoniazid Preventive Therapy (IPT) compared to deferred IPT (12 weeks at post-partum) in pregnant women with HIV
Bibliography: (see reference *62*)
Overall quality of evidence rating: moderate

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immediate IPT	deferred IPT	Relative (95% CI)	Absolute (95% CI)		
Adverse pregnancy outcome (composite)												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	106/449 (23.6%)	78/460 (17.0%)	OR 1.51 (1.09 to 2.10)	66 more per 1000 (from 12 to 131 more)	Moderate	Critical
Maternal death (any cause)												
1	randomized trials	not serious	not serious	not serious	very serious [b]	none	2/477 (0.4%)	4/492 (0.8%)	RR 0.50 (0.09 to 2.73)	4 fewer per 1000 (from 7 fewer to 14 more)	Low	Critical
Hepatotoxicity												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	29/477 (6.1%)	34/479 (7.1%)	RR 0.86 (0.53 to 1.38)	10 fewer per 1000 (from 33 fewer to 27 more)	Moderate	Critical
Any Grade 3 or 4 adverse events related to treatment												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	70/477 (14.7%)	70/479 (14.6%)	RR 1.00 (0.74 to 1.36)	0 fewer per 1000 (from 38 fewer to 53 more)	Moderate	Critical
Discontinuation due to adverse drug reactions												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	16/477 (3.4%)	28/479 (5.8%)	RR 0.57 (0.31 to 1.05)	25 fewer per 1000 (from 40 fewer to 3 more)	Moderate	Critical

[a] Optimal information size not met.
[b] Large CI including both appreciable benefits and harms. Very few events.
[c] CI includes both appreciable benefit and harm.

PICO 10: Should 6 months of levofloxacin rather than other regimens or no TPT be recommended for people in contact with patients with MDR/RR-TB?

Author(s): Lawrence Mbuagbaw (McMaster University, Canada); Dennis Falzon (WHO Global Tuberculosis Programme, Switzerland); with contributions from Trinh Duong (University College London, United Kingdom); Dick Menzies (McGill University, Canada); Greg Fox (University of Sydney, Australia); Anneke Hesseling (Stellenbosch University, South Africa)

Question: 6 months of levofloxacin compared to other regimen or no TPT in people in contact with MDR/RR-TB

Setting: Two randomized controlled trials using 6 months of levofloxacin in contacts of MDR-TB in S Africa (TB CHAMP) and Viet Nam (VQUIN). We used results from a pooled analysis of individual study participant data to express estimates of effect, rather than the Bayesian analysis which to a large extent mirrored the results from the frequentist approach

Bibliography: (see references *66 and 67*)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of levofloxacin	other regimen or no TPT	Relative (95% CI)	Absolute (95% CI)		
TB incidence (assessed with: bacteriologically confirmed or clinically defined TB, TB-related death at 54 weeks)												
2	randomized trials	not serious	not serious	not serious	not serious	none	8/1474 (0.5%)	21/1483 (1.4%)	RR 0.38 (0.17 to 0.86)	9 fewer per 1000 (from 12 to 2 fewer)	High	Critical
Death (assessed with: any cause)												
2	randomized trials	not serious	not serious	not serious	very serious[a]	none	5/1476 (0.3%)	4/1487 (0.3%)	RR 1.26 (0.34 to 4.68)	1 more per 1000 (from 2 fewer to 10 more)	Low	Critical
Adverse events (follow-up: 6 months plus 21 days; assessed with: Grade 3 or above at least possibly related to study drug (TB CHAMP; under 18y))												
1	randomized trials	not serious	not serious	not serious	serious[b]	none	4/452 (0.9%)	8/469 (1.7%)	RR 0.53 (0.16 to 1.70)	8 fewer per 1000 (from 14 fewer to 12 more)	Moderate	Critical
Adverse events (follow-up: 6 months plus 30 days; assessed with: Grade 3 or above at least possibly related to study drug (VQUIN; 97% of participants >14y))												
1	randomized trials	not serious	not serious	not serious	not serious	none	10/960 (1.0%)	2/962 (0.2%)	RR 5.26 (1.16 to 23.95)	9 more per 1000 (from 0 fewer to 48 more)	High	Critical
Adverse events of any grade leading to treatment discontinuation (follow-up: 6 months plus 21 or 30 days)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	77/1412 (5.5%)	12/1431 (0.8%)	RR 6.32 (3.43 to 11.63)	45 more per 1000 (from 20 to 89 more)	High	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of levofloxacin	other regimen or no TPT	Relative (95% CI)	Absolute (95% CI)		
Treatment completion (assessed with: opposite of discontinuation)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1078/1476 (73.0%)	1233/1487 (82.9%)	RR 0.88 (0.85 to 0.92)	100 fewer per 1000 (from 124 to 66 fewer)	High	Critical
Treatment completion (assessed with: 80% or more of doses taken by 6 months)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1092/1460 (74.8%)	1248/1468 (85.0%)	RR 0.88 (0.85 to 0.91)[c]	102 fewer per 1000 (from 128 to 77 fewer)	High	Critical
Emergence of additional fluoroquinolone resistance in TB strains												
2	Randomized trials	Serious[d]	Not serious	Serious[e]	Serious[f]	None	In none of 8 strains from index-incident pairs in the VQUIN trial that were tested with whole genome sequencing was additional resistance to levofloxacin or other antimicrobials detected[d]				Very low	Important
Emergence of additional fluoroquinolone resistance in microbiome other than TB (e.g. gut flora) not measured												
–	–	–	–	–	–	–	–	–	–	–	–	Important

[a] We rated down two levels because the confidence intervals include appreciable harm and appreciable benefit: RR 1.26 (0.34 to 4.68)
[b] We rated down one level because the confidence intervals include appreciable harm and some benefit. RR 0.53 (0.16 to 1.70)
[c] Treatment completion in the levofloxacin arm was 86% in TB CHAMP (placebo arm: 86%) and 70% in VQUIN (placebo arm: 85%) – RRs 1.00 [95% CI 0.95 to 1.06] and 0.83 [0.79 to 0.87] respectively
[d] We rated down one level for risk of bias. The results are not from a randomized comparison. In VQUIN, of the 43 persons with suspected TB post-randomization, 17 had a laboratory-confirmed incident TB, in 4 of whom an isolate could not be recovered. Results were only available for 8/13. Of these 6 were in the placebo group and 2 from the LFX arm. In TB CHAMP, 14 individuals in the placebo arm and 7 in the LFX arm developed TB, of which 7 and 3 respectively with confirmed TB. No results for levofloxacin susceptibility were available for the strains isolated.
[e] We rated down one level for indirectness. Data was only available for VQUIN; all strains were from individuals aged over 15 years.
[f] We rated down one level for imprecision due to the small number of samples and zero events.

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Annex 4. GRADE evidence-to-decision tables

Older terminology used in the context of TB preventive treatment (TPT), such as latent TB infection (LTBI) and active TB, has been retained in the original text of the tables.

Contents

PICO 1: What is the prevalence of TB infection, risk of progression to TB disease and cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries? 102

PICO 2: What is the accuracy of WHO symptomatic screening to exclude TB disease in individuals with HIV on antiretroviral treatment (ART)? 114

PICO 3: What is the accuracy of symptomatic screening and/or CXR to exclude TB disease in contacts of people with pulmonary TB without HIV in high TB incidence countries? 123

PICO 4: Could interferon-γ release assays be used as an alternative to tuberculin skin tests to identify individuals most at risk of progression from TB infection to TB disease in high TB incidence settings? 133

PICO 5: Should 3-month daily rifampicin plus isoniazid (3RH) be offered as a preventive treatment option for children and adolescents <15 years of age as an alternative to 6 or 9 months isoniazid (INH) monotherapy in high TB incidence countries? 143

PICO 6: In people of all ages at risk of TB disease, does a 4-month daily rifampicin regimen safely prevent TB disease as compared with other recommended TPT regimens? 150

PICO 7: In people of all ages at risk of TB disease, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease compared to other recommended TPT regimens? 166

PICO 8: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of TB infection in high TB incidence countries? 183

PICO 9: In pregnant and postpartum women, is isoniazid preventive treatment for TB as safe as other preventive treatment regimens 194

PICO 10: Should 6 months of levofloxacin compared to other regimen or no TPT be recommended for people in contact with MDR/RR-TB? 194

PICO 1: What is the prevalence of TB infection, risk of progression to TB disease and cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries?

Problem	Identification of household contacts for diagnosis and treatment of LTBI
Option	Systematic screening and treatment for LTBI among household contacts in specific age groups
Comparison	NA
Main outcomes	Prevalence of LTBI, risk of progression to active TB and cumulative prevalence of active TB among household contacts in different age groups
Setting	High TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000)
Perspective	Health system and public health

Background

For programmatic LTBI management, the risk associated with diagnosing and treating LTBI should be weighed against the benefit. Mass population screening and treatment of LTBI are not feasible, because of insensitive tests, high cost, poor sustainability, uncertain cost–effectiveness and risks for serious and fatal side-effects. Therefore, populations at high risk for active TB should be targeted. Accordingly, WHO currently recommends systematic LTBI screening and treatment for children < 5 years who are household contacts of TB cases in high TB incidence countries with limited resources. Systematic LTBI screening and treatment are also recommended for children aged ≥ 5 years, adolescents and adults in low TB incidence countries.

Three systematic reviews were undertaken to determine whether the target age group should be extended in high TB incidence countries by measuring three outcomes among household contacts in different age groups: prevalence of LTBI, risk of progression to active TB and cumulative prevalence of active TB. These outcomes were selected because the risk for TB may reflect a higher prevalence of LTBI and an increased risk for progression from LTBI to active TB.

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	Globally in 2015, there were an estimated 10.4 million incident cases of TB and 1.8 million deaths from TB. Management of LTBI is critical in order to end the global TB epidemic, as stated in the WHO End TB Strategy. Active TB must be excluded before TPT is given. Although WHO currently recommends systematic LTBI screening and treatment of household contacts of any age in low TB incidence countries, it is recommended only for child household contacts < 5 years in high TB incidence countries.	
Balance of effects	Do the benefits outweigh the harms? ● Yes ○ No ○ They are equal ○ Uncertain	We updated three systematic reviews conducted for the previous LTBI guidelines, focusing on household contacts. The first review addressed the prevalence of LTBI among household contacts by age group, the second the risk of progression from LTBI to active TB among household contacts and the third the cumulative prevalence of active TB among household contacts, irrespective of baseline LTBI status. In most of the studies, prevalent TB cases were those identified at the baseline visit, and those identified later were counted as incident cases. The incidence of TB therefore depended on the timing of the baseline visit relative to the diagnosis of the index case; focusing on incident TB cases, therefore, may introduce bias. In the second and third reviews, both prevalent TB during the baseline visit and incident TB during follow-up were included in the numerator. We estimated the prevalence ratios by comparing the prevalence of LTBI among household contacts by age stratum, with children < 5 years as the reference group.	

Judgement	Research evidence	Additional considerations
Balance of effects	**Pooled estimates of prevalence of LTBI among household contacts by age stratum as compared with children < 5 years in high TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000)**	

Age group (years)	No. of studies (no. of participants)	Prevalence ratio (95% CI)
0–4	–	1.0 (reference)
5–9	14	1.62 (1.25 ; 2.11)
10–14	11 (18 033)	2.33 (1.55 ; 3.5)
5–14	16 (13 867)	1.32 (1.11 ; 1.56)
≥ 15	19 (28 725)	2.04 (1.53 ; 2.63)

The analysis suggested that the prevalence of LTBI increases with age. Furthermore, we estimated risk ratios for:

- development of active TB among household contacts with LTBI and
- cumulative prevalence of active TB irrespective of baseline LTBI status, by age stratum, with children aged < 5 years as the reference.

The cumulative prevalence of active TB includes cases diagnosed during contact investigations at baseline and incident cases that developed thereafter. The table below summarizes the results of the two analyses.

Pooled estimates of risk for active TB among household contacts stratified by age and baseline LTBI status

	Baseline LTBI status positive		Regardless of baseline LTBI status	
Age (years)	No. of studies (no. of participants)	Risk ratio (95% CI)	No. of studies (no. of participants)	Risk ratio (95% CI)
0–4	–	1.0 (reference)	–	1.0 (reference)
5–14	4 (1959)	0.28 (0.12 ; 0.65)	6 (7292)	0.39 (0.18 ; 0.85)
≥15	3 (5 341)	0.22 (0.08 ; 0.60)	4 (13 620)	0.68 (0.56 ; 0.83)

The review consistently showed that older household contacts are at lower risk of development of active TB than children aged < 5 years. In the second and third reviews, we compared the risk of active TB among household contacts stratified by age group and compared with the general population, with year-adjusted national estimated TB incidence from WHO.

	Judgement	Research evidence	Additional considerations
Balance of effects		**Pooled estimates of risk of developing active TB among household contacts stratified by age and baseline LTBI status compared with the general population.**	

	Baseline LTBI status positive				Regardless of baseline LTBI status			
	Follow-up <12 months		Follow-up <24 months		Follow-up <12 months		Follow-up <24 months	
Age (years)	No. of studies (no. of participants)	Risk ratio (95% CI)	#studies (no. of participants)	Risk ratio (95% CI)	#studies (no. of participants)	Risk ratio (95% CI)	#studies (no. of participants)	Risk ratio (95% CI)
General population	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)
0–4	2 (265)	24.32 (0.73; 811.02)	3 (585)	22.87 (7.65; 68.63)	3 (1 930)	25.86 (16.87; 39.66)	5 (2 773)	14.8 (9.82; 22.3)
5–9	1 (298)	30.98 (14.26; 67.31)	1 (298)	15.49 (7.89; 30.4)	1 (1 464)	18.39 (9.75; 34.68)	1 (1 464)	9.2 (5.55; 15.23)
10–14	1 (363)	55.1 (28.55; 106.33)	1 (363)	27.55 (16.16; 46.96)	1 (1 340)	25.83 (13.97; 47.76)	1 (1 340)	12.92 (8.0; 20.86)
5–14	2 (728)	27.13 (17.47; 54.07)	3 (1 203)	8.22 (2.3; 29.36)	3 (3 067)	24.11 (16.89; 34.43)	5 (4 197)	6.29 (2.88; 13.72)
≥15	1 (3 879)	30.74 (17.46; 54.07)	2 (4 450)	13.35 (9.46; 18.83)	1 (9 380)	24.68 (14.18; 42.98)	3 (10 531)	11.67 (7.55; 18.02)

The results show that household contacts are at substantially higher risk of active TB than the general population, regardless of their age.

Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
Values	Is there important uncertainty about or variation in how much people value the main outcomes? ○ Important uncertainty or variation ○ No important uncertainty or variation ● Minimal uncertainty	We conducted an online survey *(1)* to solicit the values and preferences of individuals affected by the recommendations. Responses were provided by from 142 respondents with a median age of 46 years (interquartile range [IQR]: 37–54 years). More than 80% of the respondents reported that they would strongly or somewhat prefer to receive TPT if they were in contact with a person with active TB in the household. Similarly, of 59 respondents with children, more than 80% would strongly or somewhat prefer to give preventive treatment to their children, regardless of the children's age.	Concern about whether the respondents in the online survey correctly reflects the values of clients.

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know		National programmes could build upon existing programmes for children < 5 years, which could reduce the additional resource requirements.
Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies	A systematic review of the cost–effectiveness of management of LTBI was undertaken for the 2015 WHO LTBI guidelines. The review covered six studies of contacts of patients with active TB, all in low TB incidence countries; none provide the specific age groups of contacts. These studies suggested that screening and treatment of LTBI among contacts may save costs for the health-care system and/or have a favourable incremental cost–effectiveness ratio.	Cost–effectiveness data for low TB incidence countries may not be applicable to high TB incidence countries, where the risk for re-infection is high. The GDG noted, however, data that suggest the durability of protection in high TB incidence countries. A recent modelling study suggested that preventive treatment without LTBI testing is cost–effective for child contacts < 5 years old *(2)*.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know		

	Judgement	Research evidence	Additional considerations
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ● Yes ○ Varies ○ Don't know		Might be acceptable to key stakeholders, including health workers and programme managers; however, extension of the target age group might add a burden for national programmes that are struggling even to provide preventive treatment for child household contacts < 5 years.
Feasibility	Is the intervention feasible to implement? ○ No ○ Yes ● Varies ○ Don't know		Depends on setting, health infrastructure (e.g. availability of test and drugs) and population groups (e.g. adolescents).

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Unknown**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No studies**	
Values	**Important uncertainty or variation**		**Minimal uncertainty**	**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Unknown**	
Cost–effectiveness	**Favours the comparison**		**Favours neither the intervention nor the comparison**		**Favours the intervention**	**Varies**	**No studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Unknown**	
Acceptability	**No**			**Yes**		**Varies**	**Unknown**	
Feasibility	**No**			**Yes**		**Varies**	**Unknown**	

Conclusions

What is the prevalence of TB infection, risk of progression to TB disease and cumulative prevalence of TB disease among household contacts without HIV in different age groups in high TB incidence countries?

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TPT. *(Conditional recommendation, low-quality evidence.)* *Remark: Appropriate clinical evaluation should include assessment of the intensity of and risk for exposure, the risk for development of active TB and/or ascertainment of infection by testing for LTBI.*		
Justification	The GDG agreed that, overall, the potential benefits of preventive treatment for household contacts outweigh the harm, regardless of age, given the high risk for development of active TB disease. The GDG also noted that the balance of benefits and harm depends on confirmation of infection by LTBI testing, and the benefits would be greater in household contacts with a positive LTBI test. There was consensus that more resources would be required and that there was lack of evidence of cost–effectiveness. A systematic review suggested that screening and treatment of LTBI among contacts may save costs for the health-care system or have a favourable incremental cost–effectiveness ratio. Six of the studies were conducted in low-TB incidence countries, however, and the GDG noted that the results are not applicable to high TB incidence countries, where the risk for re-infection is high. The GDG also noted evidence of the durability of protection in high TB incidence countries. The GDG further noted that national programmes could build upon existing programmes for children < 5 years, which could reduce the additional resources required. There was consensus that preventive treatment for household contacts could be acceptable to key stakeholders, including health workers and programme managers, although extension of the target age group could add a burden to national programmes that are struggling even to implement preventive treatment for children < 5 years.		
Subgroup considerations			
Implementation considerations	In order to ensure that the benefits of preventive treatment outweigh the harm, careful clinical assessment of the intensity of and risk for exposure, of the risk for development of active TB and/or with LTBI testing are required. Active TB must be excluded before preventive treatment is given. It is important to provide support for adherence adapted to the local context to ensure completion of treatment. This may be particularly challenging for certain populations such as adolescents. The support should take into account their needs. National programmes should ensure the availability of tests and drugs and properly train health-care workers to provide preventive treatment for household contacts of all ages.		
Monitoring and evaluation			
Research priorities	Methods to improve adherence and completion rate. Implementation research to improve effectiveness and efficiency of managing household contacts (e.g. household-based intervention to reduce barriers). Development of diagnostic tests with improved performance and predictive value for reactivation of TB. Durability of protection by preventive treatment in settings endemic for TB.		

GRADE tables: SR1

SR1. Risk for TB infection among household contacts by age stratum: high TB incidence countries

Quality assessment						No. LTBI+/no. tested		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
Age groups compared: 5–10 years vs 0–5 years											
14 studies *(3–16)*	Cross-sectional	Not serious[a,b]	Serious[c]	Not serious	Not serious[d]	2265/8507	1298/9526	1.62 (1.25 ; 2.11)	85.1 (34.2 ; 151.1)	Moderate	Important
Age groups compared: 10–15 years vs 0–5 years											
11 studies *(3,5,7,9,10–16)*	Cross-sectional	Not serious[e]	Serious[f]	Not serious	Not serious[g]	2616/6782	1093/9005	2.33 (1.55 ; 3.5)	161.6 (67.2 ; 303.3)	Moderate	Important
Age groups compared: 5–15 years vs 0–5 years											
16 studies[h]	Cross-sectional	Serious[i]	Serious[j]	Not serious	Not serious[k]	3709/8772	1605/5095	1.32 (1.11 ; 1.56)	99.7 (34.9 ; 176.5)	Low	Important
Age groups compared: > 15 years vs 0–5 years											
19 studies[l]	Cross-sectional	Not serious[m]	Serious[n]	Not serious	Not serious[o]	13218/21962	1979/6763	2.04 (1.53 ; 2.63)	293.9 (155.1 ; 475.7)	Moderate	Important

[a] Potential selection bias in *(4)*, as only 69% of participants were household contacts.
[b] Potential misclassification: Eight studies *(5–6,9,12,13,15,16)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data for calculation of the number of household contacts with active TB per age stratum.
[c] High heterogeneity among studies (I^2 = 94%), probably due to differences in background TB incidence. The risk ratios of two studies *(3,7)* showed opposite effects.
[d] Small sample size in *(7)* (n < 50).
[e] Potential misclassification: Reports of seven studies *(5,7,9,12,13,15,16)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data for calculation of the number of household contacts with active TB per age stratum.
[f] High heterogeneity among studies (I^2 = 97%) probably due to differences in background TB incidence. The risk ratio in one study *(7)* showed the opposite effect.
[g] Wide 95% CI of pooled risk ratio. Small sample size in *(7)* (n < 50) and *(13)* (n < 100).
[h] Studies included: *(5,7,10,12,14,17–27)*.
[i] Potential selection bias in *(18)*, as only 89% of participants were household contacts.
[j] High heterogeneity among studies (I^2 = 93%), probably due to differences in background TB incidence. The risk ratios in three studies *(7,20,22)* showed opposite effects.
[k] Small sample size in *(7)* and *(19)* (n < 50).
[l] Studies included: *(5–7,10–12,14–17,20–28)*.
[m] Potential misclassification: The reports of ten studies *(5–7,12,13,16,21,22,25,28)* did not indicate whether household contacts with active TB were excluded from the analysis or did not provide sufficient data for calculation of the number of household contacts with active TB per age stratum.
[n] High heterogeneity among studies (I^2 = 98%), probably due to differences in background TB incidence.
[o] Small sample size in *7* and *28* (n < 100).

SR2

SR2. Development of active TB disease in household contacts with TB infection in high TB incidence countries

Quality assessment							No. of contacts (active TB/LTBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
Age groups compared: 5–15 years vs 0–5 years												
4 *(10,15,18,24)*	Cohort	Not serious	Not serious	Serious[a]	Not serious	Serious[b]	54/1329	73/630	0.28 (0.12 ; 0.65)	83.8 (40.3 ; 102.3)	Low	Critical
Age groups compared: > 15 years vs 0–5 years												
3 *(10,15,24)*	Cohort	Not serious	Not serious	Serious[c]	Not serious	Not serious	186/4746	73/595	0.22 (0.08 ; 0.60)	95.5 (49.1 ; 112.6)	Moderate	Critical

Because there were few studies in the other categories, only data from studies in high TB incidence countries with a follow-up of 1–2 years are presented in the table.

[a] Serious inconsistencies due to heterogeneity (I^2 = 71%). One study showed an increased risk in the age group 5–15 years. This was not observed in the other studies.

[b] Few events.

[c] High heterogeneity among studies (I^2 = 89.3%), probably due to differences in background TB incidence and methods used for diagnosis of active TB.

SR3

SR3. Cumulative prevalence of TB disease in household contacts, irrespective of baseline TB infection status, in high TB incidence countries

Quality assessment							No. of contacts (active TB/total no. of contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Limitations	Inconsistency	Indirectness	Imprecision	Comparator	0–5 years	RR (95% CI)	Absolute per 1000 (95% CI)		
Age groups compared: 5–15 years vs 0–5 years												
6 *(10,15,18,19, 24,29)*[a]	Cohort	Not serious	Not serious	Serious[b]	Not serious	Not serious	131/4389	203/2903	0.39 (0.18 ; 0.85)	42.9 (10.6 ; 57.6)	Moderate	Important
Age groups compared: > 15 years vs 0–5 years												
4 *(9,14,23,28)*	Cohort	Not serious	Not serious	Not serious	Not serious	Not serious	417/10856	192/2764	0.68 (0.56 ; 0.83)	22 (12.1 ; 30.3)	High	Important

Because there were few studies in the other categories, only data from studies in high TB incidence countries with a follow-up of 1–2 years are presented in the table.

[a] One outlier study *(29)* was excluded because of uncertainty about the cases that were included (co-prevalent vs incident cases).

[b] High heterogeneity among studies (I^2 = 87.6%), probably due to differences in background TB incidence.

Comparison with the general population for SR2

Development of TB disease in household contacts with TB infection in high TB incidence countries
Comparison with the general population (follow-up, 12 months)

Quality assessment						No. of contacts (active TB/no. LTBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population[a]	RR (95% CI)	Absolute per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
2 *(10,18)*	Cohort	Serious[b]	Serious[c]	Not serious	Very serious[d]	0/35 32/230	41/10 000 13/10 000	24.32 (0.73 ; 811.02)	63 (–0.7 ; 2187.1)	Very low	Critical
Comparison: Household contacts aged 5–9 years vs general population											
1 *(10)*	Cohort	Serious[b]	Not serious	Not serious	Serious[f]	12/298	13/10 000	30.98 (14.26 ; 67.31)	39 (17.2 ; 86.2)	Low	Critical
Comparison: Household contacts aged 10–14 years vs general population											
1 *(10)*	Cohort	Serious[b]	Not serious	Not serious	Serious[f]	26/363	13/10 000	55.1 (28.55; 106.33)	70.3 (35.8 ; 136.9)	Low	Critical
Comparison: Household contacts aged 5–15 years vs general population											
2 *(10,18)*	Cohort	Serious[b]	Not serious[e]	Not serious	Serious[f]	4/67 38/661	41/10 000 13/10 000	27.13 (17.47 ; 54.07)	70.5 (21.3 ; 220.7)	Low	Critical
Comparison: Household contacts aged > 15 years vs general population											
1 *(10)*	Cohort	Serious[b]	Not serious	Not serious	Serious[f]	155/3879	13/10 000	30.74 (17.46 ; 54.07)	38.7 (21.4 ; 69)	Low	Critical

[a] LTBI does not apply to the general population.
[b] Ascertainment bias highly likely. TB cases in the general population detected passively, while TB cases in the contacts detected actively; therefore, relative and absolute risks might be overestimated. The composition of the general and the study populations differs (general population of all ages versus a specific age group).
[c] High heterogeneity (I^2 = 83.9%) among studies, probably due to differences in background TB incidence.
[d] Serious imprecision with a wide 95% CI for the effect estimates, probably due to the small study size and number of outcome events.
[e] I^2 = 72.5%, indicating moderate heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.
[f] Few events and wide 95% CI.

Development of TB disease in household contacts with TB infection in high TB incidence countries
Comparison with the general population (follow-up ≤ 24 months)[a]

Quality assessment						No. of contacts (Active TB/no. LTBI)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population[b]	RR (95% CI)	Absolute per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
3 *(10,18,24)*	Cohort	Serious[c]	Serious[d]	Not serious	Serious[e]	0/35 26/320 32/230	82/10 000 41/10 000 26/10 000	22.87 (7.65; 68.63)	108.6 (33 ; 334.6)	Very low	Important
Comparison: Household contacts aged 5–9 years vs general population											
1 *(10)*	Cohort	Serious[c]	Not serious	Not serious	Serious[e]	12/298	26/10 000	15.49 (7.89 ; 30.4)	37.7 (17.9 ; 76.4)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(24)*	Cohort	Serious[c]	Not serious	Not serious	Serious[e]	26/363	26/10 000	27.55 (16.16 ; 46.96)	69 (39.4 ; 119.5)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
3 *(10,18,24)*	Cohort	Serious[c]	Serious[f]	Not serious	Serious[e]	4/67 6/475 38/661	82/10 000 41/10 000 26/10 000	8.22 (2.3 ; 29.36)	35.8 (6.5 ; 140.8)	Very low	Important
Comparison: Household contacts aged > 15 years vs general population											
2 *(10,24)*	Cohort	Serious[c]	Not serious[g]	Not serious	Not serious	26/571 155/3879	41/10 000 26/10 000	13.35 (9.46 ; 18.83)	41.4 (28.3 ; 59.7)	Moderate	Important

[a] These comparisons are based on studies with a maximum follow-up of 24 months. The TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring over 24 months.
[b] LTBI does not apply to the general population.
[c] Ascertainment bias highly likely, because TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group). The TB incidence in the population was estimated by multiplying the annual notification rate by a factor of 2.
[d] High heterogeneity among studies (I^2 = 84.4%), probably due to differences in background TB incidence.
[e] Few events and wide 95% CI.
[f] I^2 = 88.1%, indicating high heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.
[g] I^2 = 16%.

Comparison with the general population for SR3

Cumulative prevalence of TB in household contacts, irrespective of baseline TB infection status, in high TB incidence countries

Comparison with the general population (follow-up of 12 months)

Quality assessment						No. of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population	RR (95% CI)	Absolute risk per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
3 *(10,18,19)*	Cohort	Serious[a]	Not serious[b]	Not serious	Serious[c]	2/31	28/10 000	25.86 (16.87 ; 39.66)	68 (43.4 ; 105.7)	Low	Important
						9/108	41/10 000				
						73/1791	13/10 000				
Comparison: Household contacts aged 5–9 years vs general population											
1 *(10)*	Cohort	Serious[a]	Not serious	Not serious	Serious[c]	35/1464	13/10 000	18.39 (9.75 ; 34.68)	22.6 (11.4 ; 43.8)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(10)*	Cohort	Serious[a]	Not serious	Not serious	Serious[c]	45/1340	13/10 000	25.83 (13.97 ; 47.76)	32.3 (16.9 ; 60.8)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
3 *(10,18,19)*	Cohort	Serious[a]	Not serious[b]	Not serious	Serious[c]	8/102	28/10 000	24.11 (16.89 ; 34.43)	63.2 (43.4 ; 91.4)	Low	Important
						16/161	41/10 000				
						80/2804	13/10 000				
Comparison: Household contacts aged > 15 years vs general population											
1 *(10)*	Cohort	Serious[a]	Not serious	Not serious	Not serious	301/9380	13/10 000	24.68 (14.18 ; 42.98)	30.8 (17.1 ; 54.6)	Moderate	Important

[a] Ascertainment bias highly likely, because TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group).

[b] $I^2 = 0\%$.

[c] Few events and wide 95% CI.