Latent tuberculosis infection

Updated and consolidated guidelines for programmatic management

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World Health Organization

Contents

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Declaration and management of conflicts of interest

All the contributors completed a WHO declaration of interests form. All the declarations were evaluated by three members of the Steering Group for any financial conflict of interest that might warrant exclusion from membership of the Guidelines Development or Peer Review Group or from discussions during preparation of the guidelines. Intellectual conflict of interest was not considered a motive for exclusion from membership of the Guidelines Development Group, as broad expertise on latent tuberculosis (TB) was considered a criterion for selection. In addition, the diversity and representation in the Group was considered large enough to balance and overcome any potential intellectual conflict of interest. The biographies of the GDG members were made public before the meeting, in line with WHO's policy on conflicts of interest. The completed forms were reviewed at the beginning of the meeting of the Guidelines Development Group, at which time members could update their declarations.

Guidelines Development Group

The following Guidelines Development Group members declared interests, which were judged to be in no conflict with the policy of WHO or the objectives of the meeting; none of the members declared commercial financial interests that were directly or indirectly related to the objectives of the meeting.

- Padmapriyadarsini Chandrasekaran declared that her employer received research grants for the Model DOTS Project from USAID.

- Diana Gibb declared that she was coordinating a trial centre for the TB CHAMP trial, which is funded by the Medical Research Council, the Department for International Development and the Wellcome Trust.

- Stephen Graham declared that he had received remuneration from the Challenge TB for providing technical assistance in training and implementation of child contact screening and preventive therapy in Viet Nam between 2012 and 2016. He is currently a co-investigator in the V-QUIN and received research grants from the National Health and Medical Research Council, Australia. He is also a co-principal investigator of the DETECT Child TB (child TB diagnosis, treatment and prevention) in Uganda and received research grants from ELMA Philanthropies and the International Union Against Tuberculosis and Lung Disease.

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

- Marieke van der Werf declared that she was an employee of the European Centre for Disease Prevention and Control, which has an interest in the management of LTBI. She was an opponent in defense of a PhD thesis that included studies on LTBI and received a remuneration of DKK 6741.16.

- Wim Vandevelde declared that he was the chair of the Global TB Community Advisory Board on a voluntary basis. He stated that he represented the interests and needs of communities affected by TB.

The remaining members of the Group declared no conflicts of interests.

External Review Group

The following External Review Group member declared interests that were judged to be in no conflict with the policy of WHO:

- Michael Kimerling declared that his employer received grants for research on a 3-month regimen of weekly rifapentine plus isoniazid from USAID and for implementation of the regimen from UNITAID.

The remaining members of the Group declared no conflicts of interests.

Evidence reviewers

The researchers who did the systematic reviews of evidence (patients, intervention, comparator and outcomes, PICO) for these guidelines were:

- PICO 1: Darshini Govindasamy, South African Medical Research Council, South Africa; Katharina Kranzer, London School of Hygiene and Tropical Medicine, United Kingdom; and Ioana Diana Olaru, Borstel Research Centre, Germany

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- PICO 6 and 7: Yohhei Hamada, and Karl Schenkel, Global TB Programme, WHO

These reviewers did not participate in formulating the recommendations for policy.

The following reviewers declared interests that were judged not to be in conflict with the policy of WHO or the objectives of the meeting:

- Darshini Govindasamy declared that her institution (South African Medical Research Council) and research unit received grants from funders to conduct studies on TB.

- Katharina Kranzer declared that she was employed as a consultant to the national reference laboratory (Borstel Research Centre). Funding for her to speak at several German universities, Gilead, Thermo Fisher Scientific and Roche, was paid to her employer. None of these activities were considered to be a significant conflict of interests in view of the topic of the review and the nature of the work she did. Furthermore, the presence of two other reviewers on the team, that selected papers and entered and analysed data, would overcome any potential conflict of interests.

The other evidence reviewers declared no conflict of interests.

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

Abbreviations

ART   antiretroviral treatment

BCG   bacille Calmette-Guérin

CI   confidence interval

GDG   Guideline Development Group

GRADE   grading of recommendations assessment, development and evaluation

IGRA   interferon-gamma release assay

IPT   isoniazid preventive therapy or treatment

LTBI   latent tuberculosis infection

MDR-TB   multidrug-resistant tuberculosis

PICO   patients, intervention, comparator and outcomes

RCT   randomized controlled trial

TST   tuberculin skin test

TB   tuberculosis

Definitions

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

Adolescent: A person aged 10–19 years

Adult: A person over 19 years of age

Bacteriologically confirmed TB: TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-approved molecular test such as Xpert MTB/RIF

Child: A person under 10 years

Contact: Any person who was exposed to a case of TB (see definition below)

Contact investigation: A systematic process for identifying previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal includes testing for LTBI to identify candidates for preventive treatment. Contact investigation consists of identification and prioritization and clinical evaluation.

High-TB-incidence country: A country with a WHO-estimated TB incidence rate of ≥ 100/100 000

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

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

Infant: A child under 1 year of age

Latent tuberculosis infection (LTBI): A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB. There is no gold standard test for direct identification of *Mycobacterium tuberculosis* infection in humans. The vast majority of infected people have no signs or symptoms of TB but are at risk for active TB disease.

Low-TB-incidence country: Country with a WHO-estimated TB incidence rate of < 100 per 100 000 population

Preventive treatment: Treatment offered to individuals who are considered to be at risk for TB disease in order to reduce that risk. Also referred to as LTBI treatment or preventive therapy

Tuberculosis (TB): The disease state due to *Mycobacterium tuberculosis*. In this document, commonly referred to as "active" TB or TB "disease" in order to distinguish it from LTBI

Executive summary

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB. There is no gold standard test for LTBI. The WHO guidelines on LTBI consider the probability of progression to active TB disease in a specific risk group, the epidemiology and burden of TB, the availability of resources and the likelihood of a broad public health impact. Two fragmented recommendations have been made for the management of LTBI, which resulted in a number of guideline documents, posing a challenge to implementation. Therefore, several WHO Member States requested consolidated guidelines on LTBI management.

The updated, consolidated guidelines in this document respond to that request. They provide a comprehensive set of WHO recommendations for programmatic management of LTBI and the basis and rationale for national guidelines. These guidelines supersede previous WHO policy documents on the management of LTBI in people living with HIV and household contacts of people with TB and other at-risk groups. The guidelines were prepared in accordance with the requirements and recommended process of the WHO Guideline Review Committee. Seven systematic reviews were conducted to update the recommendations and make new ones. The Guideline Development Group considered the quality of the evidence, benefits and harms, values and preferences, equity, costs, acceptability and feasibility of implementation in formulating the recommendations and determining their strength.

The recommendations are presented logically according to the cascade of care for managing LTBI: identification of at-risk populations (adults and children living with HIV, HIV-negative adult and child contacts and other HIV-negative at-risk groups), ruling out active TB disease, testing for LTBI, providing treatment, monitoring adverse events, adherence and completion of treatment and monitoring and evaluation. The recommendations are categorized as: existing ones previously approved by the review committee and published, which are still valid; updated recommendations that were previously approved by the review committee but for which the evidence was reviewed, discussed with the Guidelines Development Group (GDG) and updated (including for clarity); and new recommendations. There are 10 existing, 7 updated and 7 new recommendations.

In general, the GDG reviewed the evidence from the systematic reviews and discussed each population risk group identified in detail for the prevalence of LTBI, the risk for progression to active TB and the incidence of active TB as compared with that in the general population. The GDG used the guiding principle that individual benefit outweighs risk as the mainstay of recommendations on LTBI testing and treatment. The GDG found clear evidence for the benefit of systematic testing and treatment of LTBI for people living with HIV and infants and children under 5 years of age who are household contacts of pulmonary TB patients, in all settings, regardless of the background epidemiology of TB. Similarly, they concluded that HIV-negative groups at clinical risk, such as patients initiating anti-TNF treatment, receiving dialysis, preparing for organ or haematological transplantation and those with silicosis would also benefit from testing and treatment of LTBI, regardless of the background TB epidemiology, because of their increased risk of progression to active TB disease.

The specific recommendations are given below.

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

Adults, adolescents, children and infants living with HIV

■ Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression

and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women. *(Strong recommendation, high-quality evidence. Existing recommendation)*

■ Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*

■ Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB. *(Strong recommendation, low-quality evidence. Existing recommendation)*

■ All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months. *(Conditional recommendation, low-quality evidence. Existing recommendation)*

HIV-negative household contacts

■ HIV-negative 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. *(Strong recommendation, high-quality evidence. Updated recommendation)*

■ In countries with a low TB incidence, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI. *(Strong recommendation, high–moderate-quality evidence. Existing 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 TB preventive treatment. *(Conditional recommendation, low-quality evidence.* **New recommendation***)*

Other HIV-negative at-risk groups

■ Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI. *(Strong recommendation, low–very low-quality evidence. Updated recommendation)*

■ In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. *(Conditional recommendation, low–very low-quality evidence. Existing recommendation)*

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

B. Algorithms to rule out active TB disease

■ 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. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*

■ Chest radiography may be offered to people living with HIV and on ART and preventive treatment given to those with no abnormal radiographic findings. *(Conditional recommendation, low-quality evidence.* **New recommendation***)*

■ 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 that cause such symptoms. (*Strong recommendation, moderate-quality evidence. Updated recommendation*)

■ Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age. (*Strong recommendation, low-quality evidence. Updated recommendation*)

■ 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 at-risk groups before preventive treatment. (*Conditional recommendation, very low-quality evidence.* **New recommendation**)

C. Testing for LTBI

■ Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. (*Strong recommendation, very low-quality evidence.* **New recommendation**)

■ People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals. (*Strong recommendation, high-quality evidence. Existing recommendation*)

■ LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years. (*Strong recommendation, moderate-quality evidence. Updated recommendation*)

D. Treatment options for LTBI

■ Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. (*Strong recommendation, high-quality evidence. Existing recommendation*)

■ Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. (*Strong recommendation, low-quality evidence.* **New recommendation**)

■ Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. (*Conditional recommendation, moderate-quality evidence.* **New recommendation**)

■ The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone. (*Strong recommendation, moderate–high-quality evidence. Existing recommendation*)

■ In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy. (*Conditional recommendation, low-quality evidence. Existing recommendation*).

E. Preventive treatment for contacts of patients with multidrug-resistant-TB

■ In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. (*Conditional recommendation, very low-quality evidence.* **New recommendation**)

Important additional considerations

Adverse events monitoring

The risk for adverse events during preventive treatment must be minimized. Individuals receiving treatment for LTBI should be monitored routinely and regularly at monthly visits to health care providers. The prescribing health care provider should explain the disease process and the rationale for the treatment and emphasize the importance of completing it. People receiving treatment should be urged to contact their health care providers if they develop symptoms between visits, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should immediately stop treatment.

Adherence and completion of preventive treatment

Adherence to the full course and completion of treatment are important determinants of clinical benefit, both to the individual and to the success of the programme. Interventions should be tailored to the specific needs of the risk groups and to the local context to ensure adherence and completion of treatment.

Programmatic management, monitoring and evaluation

The national programme should prepare a national plan for programmatic management of LTBI, including prioritizing groups identified as being at high risk on the basis of local epidemiology and the health system. They should create a conducive environment for the policy and the programme, including national and local policies and standard operating procedures to facilitate implementation of the recommendations in these guidelines. Programmatic management of LTBI should include monitoring and evaluation systems that are aligned with national systems for patient monitoring and surveillance. Appropriate recording and reporting tools should be developed, with standardized indicators.

1.   Introduction

1.1   Background

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB *(1)*. As there is no "gold standard" test for LTBI, the global burden is not known with certainty; however, up to one third of the world's population is estimated to be infected with *M. tuberculosis (2–4)*, and the vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk for active TB disease and for becoming infectious. Several studies have shown that, on average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection *(5)*. The risk for active TB disease after infection depends on several factors, the most important being immunological status *(1)*.

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy *(6)*. The efficacy of currently available treatments ranges from 60% to 90% *(1)*. The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events. Mass, population-wide LTBI testing and treatment are not feasible because the tests are imperfect, there are risks of serious and fatal side-effects, and the cost would be high, for an unproven public health impact. For infected individuals in population groups in which the risk for progression to active disease significantly exceeds that of the general population, however, the benefits are greater than the harm. Management of LTBI 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 starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process.

1.2   Rationale

Current WHO guidelines on LTBI are based on the probability that the condition will progress to active TB disease in specific risk groups, on the underlying epidemiology and burden of TB, the availability of resources and the likelihood of a broader public health impact. Therefore, management of LTBI is recommended for people living with HIV *(7)* and for children under 5 years who are household contacts of people with pulmonary TB *(8)* in all settings including those with a high TB incidence (estimated annual TB incidence rate, ≥ 100 per 100 000 population) and for adult contacts of people with TB and other clinical risk groups living in settings with a low TB incidence (estimated annual TB incidence rate < 100 per 100 000 population) *(9–11)*. The cut-off point for defining a country as having a low or a high TB incidence was set by consensus by the previous Guideline Development Group (GDG) *(9, 10)*. Although their recommendations led to a significant increase in preventive treatment of TB, particularly among people living with HIV, global coverage of the intervention is still very low *(12)*. Furthermore, the fragmented recommendations resulted in a multiplicity of guideline documents, which posed challenges for smooth implementation. Therefore, several WHO Member States requested consolidated guidelines on LTBI management to ensure harmonized, smooth programmatic implementation. Increased interest has also been shown in programmatic management of LTBI as part of the End TB Strategy, including TB elimination *(13)*.

1.3   Scope

The present consolidated guidelines include a comprehensive set of WHO recommendations for the management of LTBI and will facilitate implementation of the End TB Strategy. They include updated recommendations from the 2011 WHO guidelines on intensified TB case-finding and isoniazid preventive

Guidelines that have been updated or consolidated

- Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries. Geneva: World Health Organization; 2011 (http://www.who.int/tb/features_archive/policy_statement_igra_oct2011.pdf).

- Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_ng.pdf).

- Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf).

- Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf).

- Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB and HIV-prevalence settings: 2015 update. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/174052/1/9789241508872_eng.pdf).

- Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://apps.who.int/medicinedocs/documents/s21682en/s21682en.pdf).

therapy for people living with HIV in resource-constrained settings as well as recommendations on the use of LTBI testing. Other relevant recommendations approved by the guideline review committee are also included (**Box 1**). The guidelines presented here are the most recent and most comprehensive WHO guidelines for programmatic management of LTBI. They are expected to provide the basis and rationale for the development of national guidelines for LTBI management, adapted to the national and local epidemiology of TB, the availability of resources, the health infrastructure and other national and local determinants.

1.4   Target

The guidelines are to be used primarily in national TB and HIV control programmes or their equivalents in ministries of health and for other policy-makers working on TB and HIV and infectious diseases. They are also appropriate for officials in other line ministries with work in the areas of health, including prison services, social services and immigration (such as ministries of justice or correctional services) and clinicians and public health practitioners working on TB, HIV, infectious diseases, prevention, child health and noncommunicable diseases such as chronic kidney disease and cancer.

1.5   Development of the guidelines

In conformity with the process recommended by the WHO guideline review committee *(14)*, three groups were established: a guideline steering group, composed of WHO staff, including from regional offices; the GDG, composed of a guideline methodologist, external content experts, national TB programme managers, academicians and representatives of patient groups and civil society, who provided input at all stages of the process; and the external review group, composed of experts with interest in LTBI, who reviewed the draft guidelines.

The steering group prepared the scoping document for the guidelines, which identified key questions in PICO (population, intervention, comparator, outcomes) format, the systematic reviews required as a basis for the recommendations and the process for preparing the guidelines. The group also considered questions on aspects of programmatic management of LTBI for which new evidence was likely to be available.

The following seven key questions were identified:

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

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

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

4. PICO 4:[1] Could Interferon-gamma release assays be used as an alternative to tuberculin skin tests to identify individuals most at risk of progression from LTBI to active TB in high TB incidence settings?

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

6. PICO 6: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of LTBI in high TB incidence countries?

7. PICO 7: Should preventive treatment be recommended for contacts of patients with multidrug resistant / rifampicin resistant-TB?

A list of potential outcomes of interest for each question was circulated to all members of the GDG, who scored the importance of each outcome on a scale of 1 to 9: 1–3: not important; 4–6: important; and 7–9: critical. The average of the scores for each outcome was used to prioritize the outcome and to select the most important outcomes for each PICO question. The outcomes selected for each question and the scores for their importance are presented in **Annexes 1 and 2**.

Seven new or updated systematic reviews were conducted for these guidelines. The existing recommendations were discussed in the GDG and updated, as appropriate, including for clarity, as deemed necessary. Furthermore, an online survey was conducted to determine the preferences and values of affected populations for the management of LTBI (**Annex 3**). A series of virtual meetings, co-chaired by a technical expert and a guideline methodologist, were organized to appraise the evidence for each PICO and formulate recommendations. The "evidence-to-decision" tables developed on the "GRADEpro interface" were used to guide discussions on benefits and harm, the quality of the evidence, cost, feasibility, acceptability, equity, values and preferences *(14)*. The recommendations and their strength were determined by the GDG on the basis of these factors. The guideline methodologist facilitated the discussions in order to reach consensus, which was defined as unanimous or majority agreement. Recommendations from existing WHO guidelines were initially assessed by the steering group and were later discussed and approved by the GDG. Valid recommendations that did not require updating were also included. The guidelines and the supporting documents were reviewed and endorsed by all GDG members. Remarks from the external review group were evaluated by the steering group for incorporation into the final version of the guidelines.

There are 10 existing, 7 updated and 7 new recommendations. The GRADE (grading of recommendations, assessment, development and evaluation) tables for the seven new recommendations are presented in Annex 1. The detailed evidence-to-decision tables for each PICO and the results of the systematic reviews are shown in **Annex 2** and the survey on values and preferences in **Annex 3**.

1.6   Quality of evidence and strength of the recommendations

The quality of evidence and the strength of the recommendations were assessed with the GRADE method *(15)*. In this process, the quality of a body of evidence is 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

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[1]   This PICO was not included in the original scoping document submitted to the WHO Guidelines Review Committee but was added later at the suggestion of the GDG and in agreement with the Secretariat of the guidelines review committee.

effect depends on the level of confidence in that estimate: the higher the quality of evidence, the more likely a strong recommendation can be made. A decision on the strength of the evidence also depends on other factors. The strength of a recommendation reflects the degree of confidence of the GDG that the desirable effects outweigh the undesirable effects. The desirable effects included beneficial health outcomes (e.g. prevention and early diagnosis of TB, reduced TB-related morbidity and mortality), a smaller burden of TB and more savings; whereas the undesirable effects include harm, a greater burden and more costs. The "burdens" included adherence to the recommendations by programmes, patients and caregivers (e.g. families), such as more frequent tests and taking additional medications.

The quality of evidence was categorized into four levels:

High   We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate   We are moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low   Our confidence in the effect estimate is limited: the true effect may be substantially different.

Very low   We have very little confidence in the effect estimate: the true effect is likely to be substantially different.

The recommendations in these guidelines are either strong or conditional.

A *strong* recommendation is one for which the GDG was confident that the desirable effects of adherence would outweigh the undesirable effects. This 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 would probably outweigh the undesirable effects, but 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).

1.7   Publication, implementation, evaluation and expiry

These guidelines will be published on the WHO website in at least four languages (English, French, Spanish and Russian) and can be downloaded freely. The printed guidelines will be widely distributed at international and regional conferences and meetings of programme managers in all regions. Implementation of the recommendations will be monitored regularly in the annual data collection system of WHO Global TB Data Monitoring. WHO will update the guidelines 5 years after their publication or earlier if new evidence becomes available that necessitates a revision.

1.8   Presentation of the guidelines and recommendations

The overall structure of these guidelines and the recommendations follow the logical cascade of management of LTBI: identification of at-risk populations (adults and children living with HIV, HIV-negative adult and child contacts of TB cases and other HIV-negative at-risk groups); ruling out active TB disease; testing for LTBI; providing treatment; monitoring adverse events; adherence to and completion of treatment; and monitoring and evaluation. The recommendations are categorized as *existing* (recommendations that were published in previous guidelines approved by the review committee and are still valid); *updated* (recommendations that were published in previous guidelines approved by the review committee, for which the evidence was reviewed, discussed in the GDG and updated, including for clarity); and *new* (recommendations that were made for the current guidelines).

2. Identification of populations for testing and treatment of latent tuberculosis infection

Not all individuals infected with *M. tuberculosis* develop active TB. It is estimated that the lifetime risk of an individual with LTBI for progression to active TB is 5–10% *(5)*. The risk is particularly high among children under the age of 5 years and among people with compromised immunity *(1)*. As preventive treatment entails risks and costs, preventive treatment of *M. tuberculosis* infection should be selectively targeted to the population groups at highest risk for progression to active TB disease, who would benefit most from treatment of LTBI.

In selecting at-risk populations for programmatic management of LTBI, consideration should be given to the epidemiology and pattern of transmission of TB in the country, so that treatment offers lasting protection. A critical component of programmatic management should therefore be a comprehensive individual clinical assessment that takes into account the balance between the risks and benefits for the individual receiving treatment.

This section describes at-risk populations for whom systematic LTBI testing and treatment is recommended.

2.1 Adults and adolescents living with HIV

Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women. *(Strong recommendation, high-quality evidence. Existing recommendation)*

Source of existing recommendation: Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva; World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Summary of evidence

TB is the most frequent cause of AIDS-related deaths worldwide, despite progress in access to ART *(16)*. TB caused about 400 000 deaths among people living with HIV in 2016, representing one third of all HIV deaths. Global data in 2016 indicated that people living with HIV were 21 times (95% confidence interval [95% CI] 16;27) more likely to develop active TB than those without HIV infection *(12)*.

A systematic review of 12 randomized controlled trials (RCTs) of 8578 people living with HIV *(17)* found that preventive treatment reduced the overall risk for TB by 33% (relative effect [RR] 0.67, 95% CI 0.51;0.87) among people living with HIV. For those who were 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 preventive treatment in people receiving ART. A double-blind RCT of 1329 people living with HIV and receiving ART indicated that those on ART with negative TST or IGRA benefited more from IPT than those who were TST or IGRA positive *(18)*. An RCT of 2056 people living with HIV *(19)* and follow-up data *(20)* showed additive benefits of preventive treatment plus ART in reducing both TB incidence and overall mortality. The protective effect lasted for more than 5 years *(20)*.

The GDG reviewed the evidence from the systematic reviews and discussed each population risk group identified in detail for the prevalence of LTBI, risk of progression to active TB and the incidence of active TB as compared with that in the general population. They concluded that the evidence shows a clear benefit of systematic testing and treatment of LTBI for people living with HIV.

Preventive treatment should be given to adults and adolescents living with HIV, regardless of their immune status and whether they are on ART, given the evidence of the additional protective effect with ART. A systematic review of studies conducted before ART became available showed the value of providing preventive treatment immediately after successful completion of TB treatment among people living with HIV in countries with high TB incidence *(7, 21)*. Therefore, preventive treatment is recommended for people who were previously treated for TB. No evidence was found, however, for preventive treatment of people who had successfully completed treatment for multidrug-resistant (MDR) or extensively drug-resistant TB or those who are concomitantly receiving ART.

Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the mother and the fetus *(22)*. As isoniazid and rifampicin, the drugs commonly used in preventive treatment, are safe for use in pregnant women *(23)*, pregnancy should not disqualify women living with HIV from receiving preventive treatment. Nevertheless, sound clinical judgement is required to determine the best time to provide it.

There is no evidence about repeated courses of preventive treatment, and hence no recommendation is made in the present guidelines. In settings with high TB transmission (as defined by local authorities), however, IPT for 36 months or longer is recommended conditionally *(24)* (see **section 5**). Clinical trials of repeated courses of preventive treatment are lacking and will be essential for updating these guidelines.

2.2   Infants and children living with HIV

- Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*

- Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB. *(Strong recommendation, low-quality evidence. Existing recommendation)*

- All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months. *(Conditional recommendation, low-quality evidence. Existing recommendation)*

Source of existing and updated recommendations: Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva; World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Summary of evidence

A systematic review conducted for the previous guidelines included two studies 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 *(25)*. The other RCT, however, showed no benefit of preventive treatment in HIV-infected infants with no known exposure to a TB case who were identified in the first 3–4 months of life, given rapid access to ART and carefully monitored every month for new exposure to TB or disease *(26)*.

Few RCTs included children on ART. In one trial of 167 children on ART, the incidence of TB was lower in those given preventive treatment than in those who were not, but the difference was not statistically significant (incidence rate ratio 0.51, 95% CI 0.15;1.75) *(27)*. A cohort study suggested an additive protective effect of preventive treatment in children receiving ART *(28)*.

Rationale for the recommendations

For infants aged <12 months old living with HIV, the GDG noted that preventive treatment should be given only to those infants who have a history of household contact with a person with TB and do not have TB disease according to investigations conducted in line with national guidelines because of limited data on the benefits. The GDG strongly recommended preventive treatment for children aged ≥ 12 months living with HIV, despite the low quality of the evidence, because of the clear benefits seen in adults with HIV and the high risk for active TB among people living with HIV.

The GDG noted that, although the evidence for the efficacy of preventive treatment in children on ART is limited, it is biologically plausible, given the evidence of additive effects in adults with HIV receiving ART. Thus, preventive treatment is recommended for children, regardless of whether they are on ART.

There is no evidence on the use of preventive treatment in children living with HIV after successful completion of TB treatment. Like adults, however, children living with HIV who are exposed to reinfection and recurrence of TB would benefit from preventive treatment. Therefore, based on this judgement, the GDG conditionally recommended that all children living with HIV who have been successfully treated for TB and are living in settings with high TB incidence, prevalence and transmission (as defined by national authorities) should receive a course of preventive treatment. Preventive treatment can be started immediately after the last dose of TB therapy or later, according to clinical judgement.

2.3   HIV-negative household contacts of a person with pulmonary TB

- HIV-negative 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. *(Strong recommendation, high-quality evidence. Updated recommendation)*

- In countries with a low TB incidence, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI. *(Strong recommendation, high–moderate-quality evidence. Existing 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 TB preventive treatment. *(Conditional recommendation, low-quality evidence. **New recommendation**)*

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.

Source of existing recommendation: Guidelines on the management of latent tuberculosis Infection. Geneva; World Health Organization; 2015 (http://apps.who.int/medicinedocs/documents/s21682en/s21682en.pdf).

Summary of evidence

We updated a systematic review conducted for the previous guidelines *(9, 10)*, focusing on household contacts in countries with high TB incidence. The aim of the review was to determine the prevalence of LTBI, progression to active TB disease and the cumulative prevalence of active TB among household contacts, stratified by age. We added 19 studies published between 2014 and 2016. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**.

The prevalence of LTBI was higher among children and adolescents aged > 15 years and adults than in children < 5 years, who were at greatest risk for progression to active TB disease. In comparison with child household contacts < 5 years, the pooled risk ratios for progression to active TB were lower in children aged 5–15 years (0.28, 95% CI 0.12;0.65, four studies) and for those > 15 years (0.22, 95% CI 0.08;0.60, three studies). All household contacts, regardless of their age or LTBI status, were nevertheless at substantially higher risk for progression to active TB than the general population (**Table 1**).

Table 1. Pooled estimates of risk for active TB among household contacts stratified by age and baseline LTBI status as compared with the general population

| Age (years) | LTBI-positive at baseline | | | | Regardless of baseline LTBI 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 (0.73–811.0)	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)

Rationale for the recommendations

The GDG noted the significantly higher risk of infants and young children < 5 years for developing active TB. Furthermore, the disease can develop rapidly in young children, and they are at greatest risk for severe and disseminated disease, associated with high morbidity and mortality. Therefore, the GDG strongly recommended preventive treatment for child household contacts aged < 5 years, regardless of the background epidemiology of TB, but only after active TB disease has been ruled out. Preventive treatment could also be considered conditionally 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 on-going transmission of TB. The GDG also noted that the availability of resources and the capacity of the health infrastructure to assess the intensity and the risk of exposure and development of active TB, to weigh harm and benefit and to exclude active TB disease before initiation of treatment are important considerations in the conditionality of the recommendation.

2.4 Other HIV-negative at-risk groups

- Patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for LTBI. *(Strong recommendation, low–very low-quality evidence. Updated recommendation)*

- In countries with a low TB incidence, systematic testing for and treatment of LTBI may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. *(Conditional recommendation, low–very low-quality evidence. Existing recommendation)*

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

Remark: *People should be tested and treated for LTBI with strict adherence to human rights and the strongest ethical considerations. For example, positive test results or treatment for LTBI should not affect a person's immigration status or delay the possibility of immigrating.*

Source of existing recommendations: Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://apps.who.int/medicinedocs/documents/s21682en/s21682en.pdf).

Summary of evidence

The GDG considered the three systematic reviews that were conducted for the previous LTBI guidelines to determine which of the 24 defined at-risk population groups should be priorities for LTBI testing and treatment for this update *(9, 10)*. Evidence of an increased prevalence of LTBI, an increased risk of progression from LTBI

to active TB disease and an increased incidence of active TB was available for the following 15 risk groups: adult and child TB contacts, health care workers and students, people living with HIV, patients on dialysis, immigrants from countries with a high TB burden, patients initiating anti-TNF therapy, people who use illicit drugs, prisoners, homeless people, patients receiving an organ or haematological transplant, patients with silicosis, patients with diabetes, people with harmful use of alcohol, tobacco smokers and underweight people. An increased risk for progression to active TB was reported for 4 of the 15 groups: people living with HIV, adult and child TB contacts, patients on dialysis and underweight people. Increased risks for active TB were reported for all groups except underweight people.

Rationale for the recommendations

The GDG noted that people in HIV-negative clinical risk groups, such as patients initiating anti-TNF treatment, patients on dialysis, patients preparing for organ or haematological transplant and patients with silicosis, would benefit from testing for and treatment of LTBI regardless of the background TB epidemiology, because of their increased risks for progression to active TB disease. The GDG made strong recommendations despite the low- to very low-quality evidence on the basis of its judgement that the identified at-risk population groups were at increased risk for progression to active TB disease and that the benefits of treatment outweigh the potential harm.

The GDG also concluded that the evidence for the benefits of systematic testing and treatment of LTBI might not outweigh the harm in the following population risk groups: health care workers, immigrants from countries with a high TB burden, prisoners, homeless people and people who use illicit drugs. The GDG judged, however, that the benefits might outweigh the harm to a greater extent in settings with a low TB incidence than in those with a high TB incidence because of the background TB epidemiology and the risks for transmission and reinfection. A decision to test for and treat LTBI systematically in these population groups should be made in accordance with the local TB epidemiology and context, health system structure, availability of resources and overall health priorities. Priority must be given to individuals who were recently infected with TB, as documented by conversion from negative to positive in LTBI tests (either IGRA or TST). The GDG also concluded that recent immigrants from countries with a high TB burden to one with a low burden should be prioritized. The GDG emphasized, however, that a person's status – testing positive for LTBI or receiving LTBI treatment – should not affect the process, procedure or status of immigration.

The GDG noted the paucity of data from clinical trials on the benefits and harm of systematic LTBI testing and treatment of patients with diabetes, people with harmful use of alcohol, tobacco smokers and underweight people. They concluded that the benefits of systematic, routine testing and treatment of these risk groups do not outweigh the risks, unless they are part of the groups covered in the recommendations, regardless of background TB epidemiology.

The GDG agreed that prioritization of groups on the basis of their risk and the local and national context (e.g. epidemiology, resource availability) would be acceptable to individuals and to key stakeholders, including clinicians and programme managers. It noted that the high risk for ongoing TB transmission of certain risk groups, such as health care workers (including students), prisoners (and prison staff), immigrants from high-incidence countries, homeless people and people who use illicit drugs, requires attention, so that the benefit of treatment is not compromised by reinfection.

Considerations for implementation

A decision of national TB programmes and other stakeholders on priority risk groups for programmatic management of LTBI should primarily take into account the evidence in providing a lasting prevention from progression to active TB (e.g. absence of continuous transmission and reinfection) with benefits outweighing risks to the individuals belong to the group and the efficient use of resources. The GDG noted that prioritization of at-risk groups for LTBI testing and treatment could yield savings for the health care system. The GDG noted the value of ART for preventing TB in people living with HIV, underlining the importance of ensuring provision of ART for all people living with HIV as per the current WHO policy *(29)*.

3. Algorithms for ruling out active tuberculosis disease

This section recommends algorithms for ruling out active TB disease before providing preventive treatment.

3.1 Adults, adolescents, children and infants living with HIV

3.1.1 Adults and adolescents with HIV

■ 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. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*

■ Chest radiography may be offered to people living with HIV and on ART and preventive treatment be given to those with no abnormal radiographic findings. *(Conditional recommendation, low-quality evidence.* **New recommendation***)*

■ 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 that cause such symptoms. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*

Remark: *Chest radiography should not be a requirement for initiating preventive treatment.*

Summary of evidence

Active TB disease must be excluded before initiating preventive treatment. In 2011, WHO conducted a systematic review and a meta-analysis of individual patient data and recommended a symptom-screening rule of a combination of current cough, weight loss, night sweats and fever in order to exclude active TB. 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 living with HIV who were included in studies in the systematic review were not receiving ART *(30)*.

During updating of the guidelines, we conducted a systematic review to assess the performance of the four-symptom screening rule in people living with HIV who were and were not receiving ART; 17 studies with such information were retained. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**.

The pooled sensitivity of the four-symptom screening rule for people living 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); the pooled sensitivity of the rule for people living with HIV but not receiving ART was 89.3% (95% CI 82.6;93.6), and the specificity was 27.2% (95% CI 17.3;40.0). Two studies provided data on addition of abnormal chest radiographic findings to the screening rule for people living with HIV on ART. 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 those of the symptom screen alone.

In all studies, the median prevalence of TB among people living 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 chest radiographic findings increased the negative predictive value by 0.2%.

No studies of the addition of chest radiography to the symptom rule for pregnant women were found in the review. The algorithm for TB screening in adults and adolescents living with HIV is shown in **Fig. 1**.

Fig. 1   Algorithm for screening adults and adolescents living with HIV for TB

Adults and adolescents living with HIV[a]

Screen people with any of the following symptoms of TB:[b]
Current cough
Fever
Weight loss
Night sweats

No — Assess for contraindications to preventive treatment[c]

- No → Give preventive treatment
- Yes → Defer preventive treatment (also screen for TB at follow-up)

Yes — Investigate for TB and other diseases[d]

- Other diagnosis → Give appropriate treatment and consider preventive treatment
- Not TB → Follow up and consider preventive treatment
- TB → Treat for TB[e]

Screen for TB regularly, at each encounter with a health worker or visit to a health facility

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[a] Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritized to reduce *M. tuberculosis* transmission in all settings in which care is provided.

[b] Chest radiography can be done if available, particularly for people living with HIV on ART, but is not required to classify patients into TB and non-TB groups. In settings with a high HIV prevalence and a high TB prevalence among people living with HIV (e.g. > 10%), strong consideration should be given to adding other, sensitive investigations.

[c] Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. History of TB and current pregnancy should not be contraindications for starting preventive treatment. Although LTBI testing is not a requirement for initiating preventive treatment, it may be done as a part of eligibility screening where feasible.

[d] Xpert MTB/RIF should be used as the initial diagnostic test for TB. Detailed algorithms for people living with HIV suspected of having TB are available in the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf).

[e] Resume regular screening for TB after completion of treatment for active disease.

Rationale for the recommendations

Overall, the GDG agreed that the four-symptom screening rule is very useful for ruling out active TB before providing preventive treatment to people living with HIV, regardless of whether they receive ART. It noted the potential benefits of adding an abnormal chest radiographic finding to the four-symptom screening rule, while recognizing a marginal improvement in performance. Moreover, increased use of chest radiography 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 chest radiography should be added as an additional investigation only if it does not pose a barrier to the provision of preventive treatment for people living with HIV. Although no study was found of the additive role of chest radiography in testing pregnant women, the GDG noted that pregnant women living with HIV could also benefit, as long as good clinical practices are observed to prevent any significant risk to the fetus *(31)*.

3.1.2 Children living with HIV

> Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a case of TB should be evaluated for TB and other diseases that cause such symptoms. If the evaluation shows no TB, these children should be offered preventive treatment, regardless of their age. *(Strong recommendation, low-quality evidence. Updated recommendation)*
>
> *Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight-for-age < –2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening,*
>
> *Children and infants < 1 year of age should be given preventive treatment only if they have a history of household contact with a TB case and active TB has been excluded in investigations.*

Summary of evidence

Infants and children living with HIV should be screened for TB routinely, as part of standard clinical care, regardless of whether they are receiving TB prophylaxis or ART. A systematic review conducted for the previous guidelines identified limited evidence on the best approach to screening infants and children for TB *(7)*. On the basis of these few studies and expert opinion, the previous guidelines group recommended a screening rule consisting of poor weight gain, fever, current cough and a history of contact with a TB case. We conducted a new systematic review to assess the performance of this screening rule. The only publication found was the conference abstract of a study of 176 hospitalized children with HIV aged ≤ 12 years in Kenya *(32)*. The study had a sensitivity of 100% (95% CI, 76.8;100.0) and a specificity of 4.3% (95% CI, 1.8;8.7).

Rationale for the recommendation

The GDG noted the paucity of data on the usefulness of the screening rule for children living with HIV. The single study showed that the symptom screening rule currently recommended for children with HIV performs well, but no study has been reported on the harm or challenges of the rule, such as resource requirements for implementation. Symptom-based screening is generally accepted by clients and is feasible in resource-constraint settings.

Therefore, the GDG decided to make the same strong recommendation. Children living with HIV who screen positive for TB may have TB and should be evaluated for TB and other diseases. If the evaluation shows no TB, children with HIV should be offered preventive treatment, regardless of their age, while only infants < 12 months of age who have a history of household contact with a person with TB and have been investigated for TB according to national guidelines should receive preventive treatment. 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. The algorithm for TB screening in children aged ≥ 1 year living with HIV is shown in **Fig. 2**.

3.2 HIV-negative infants, children and adults who are household contacts of a person with pulmonary TB

3.2.1 HIV-negative infants and children < 5 years of age

Summary of evidence

We updated a previous systematic review of screening algorithms for HIV-negative people and people with unknown HIV status *(33)*. The review revealed only one study of young children (mean age, 19.2 months) in which various symptoms were evaluated, such as failure to thrive and prolonged cough. The report did not discuss the combination of symptoms for excluding TB *(34)*.

Fig. 3 is a simple algorithm for ruling out active TB in child household contacts aged < 5 years before preventive treatment *(8)*. The algorithm can be used by health workers at peripheral level. Research on symptom-based screening of children's TB contacts indicates that this contact management strategy is safe and more feasible in resource-limited settings than contact screening based on diagnoses *(35, 36)*. Furthermore, a recent modelling

Fig. 2   Algorithm for screening children aged ≥ 1 year living with HIV for TB
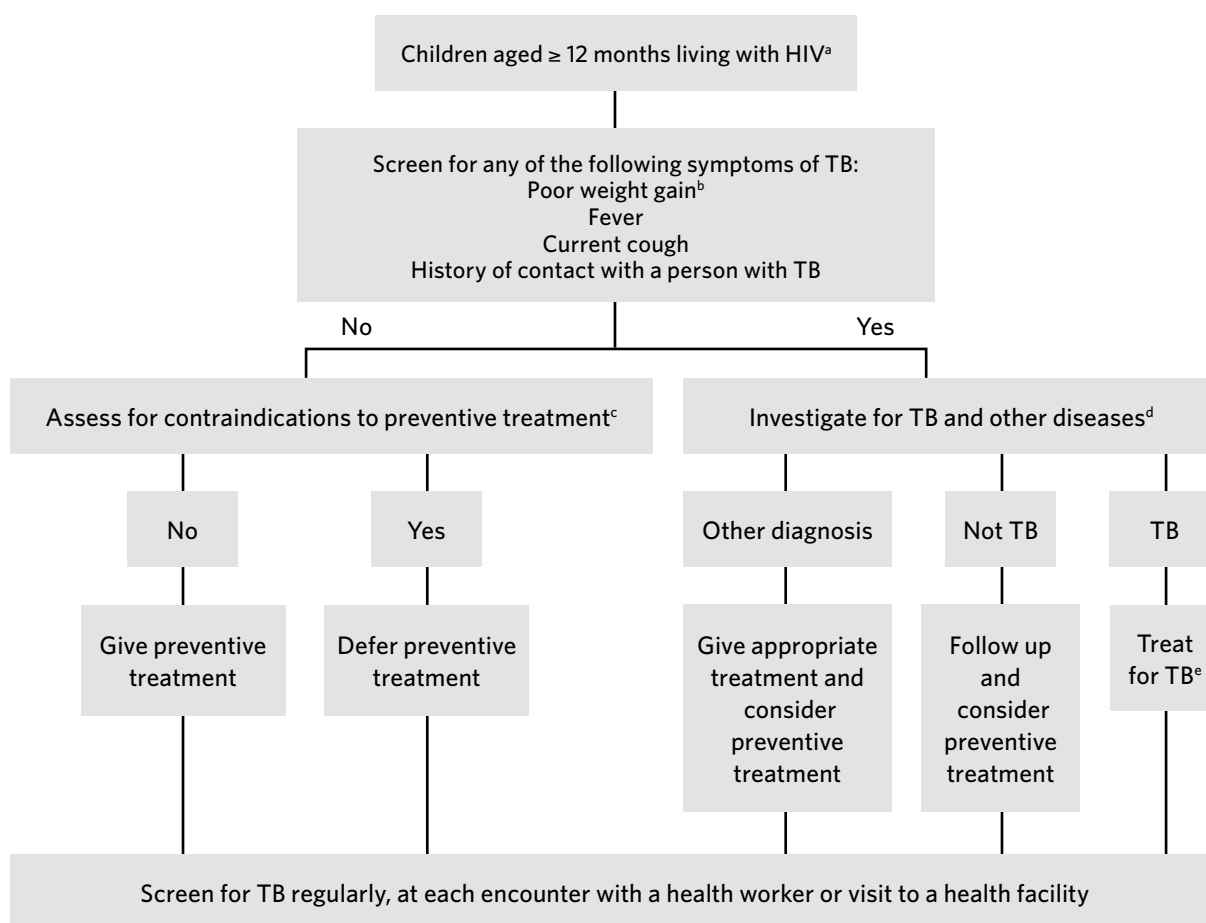
a   All infants < 1 year of age should be given preventive treatment if they have a history of household contact with a TB case.
b   Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight-for-age < –2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening.
c   Contraindications include active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A history of TB should not be a contraindication for starting preventive treatment. Although LTBI testing is not a requirement for initiating preventive treatment, it may be done as a part of eligibility screening where feasible.
d   Xpert MTB/RIF should be used as the initial diagnostic test for TB. Detailed algorithms for people living with HIV who have suspected TB are available in the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf).
e   Resume regular screening for TB after completion of treatment for active disease.

study suggested that providing preventive treatment without LTBI testing is cost-effective for child contacts under 5 years of age *(37)*.

3.2.2 HIV-negative household contacts aged ≥ 5 years and other at-risk groups

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 at-risk groups before preventive treatment. *(Conditional recommendation, very low-quality evidence. **New recommendation**)*

Summary of evidence

We updated the previous systematic review used for the 2015 guidelines *(9, 10)* to determine the sensitivity and specificity of screening based on symptoms and/or chest radiography for ruling out active TB in HIV-

Fig. 3   Algorithm for screening HIV-negative infants and children < 5 years of age who are household contacts of people with TB
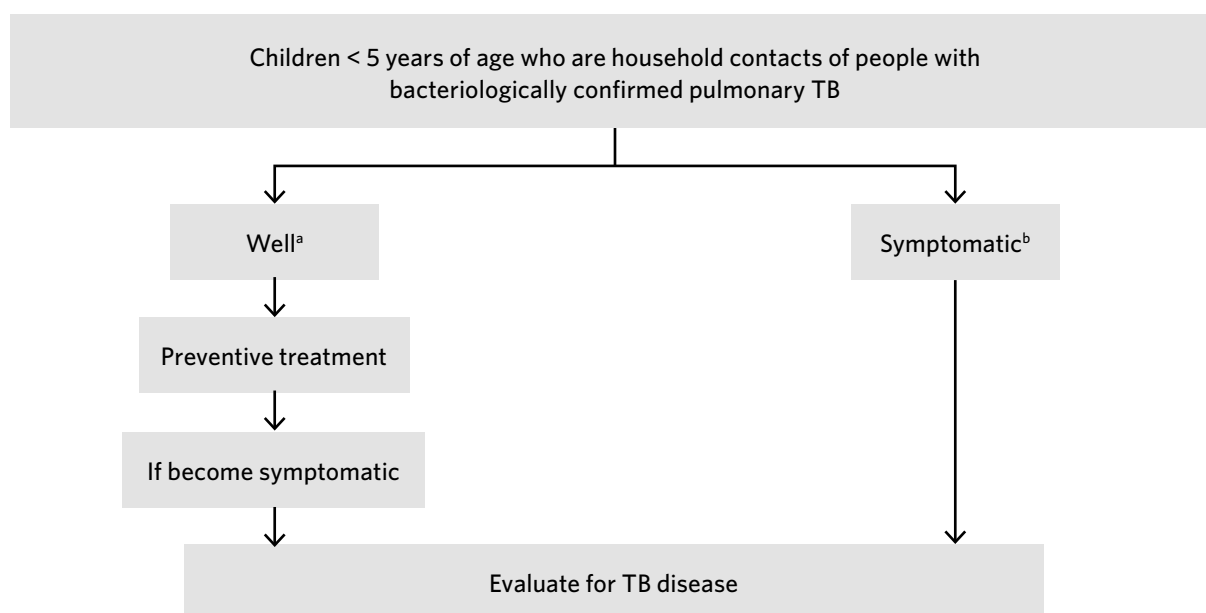
a   Children must be free of any TB and non-TB related symptoms to be considered well.
b   The commonest TB-related symptoms are persistence of: cough, fever, not eating well/anorexia, weight loss/failure to thrive, fatigue, reduced playfulness and decreased activity. If TB disease is suspected, refer to Chapter 3 in the Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition (www.who.int/tb/publications/childtb_guidelines/en/).
c   Isoniazid 10 mg/kg (7–15 mg/kg) daily for 6 months. 3-month weekly regimen of rifapentine plus isoniazid or 3-month daily rifampicin plus isoniazid may be used as an alternative (see section 5).
d   If TB disease is diagnosed, anti-TB treatment should be started and the child registered with the national TB programme. If TB disease is excluded, the child should be considered for eligibility for preventive treatment.

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negative people and people of unknown HIV status. The review covered 33 studies, including 17 newly identified. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**. To illustrate how the various screening and diagnostic algorithms are expected to rule out active TB, 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) chest radiographic abnormality suggestive of TB, (v) any chest radiographic abnormality and (vi) a combination of any chest radiographic abnormality or any TB symptom. The model suggested that the combination of any chest radiographic abnormality and the presence of any symptoms suggestive of TB (i.e. any cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) would offer the highest sensitivity (100%) and negative predictive value (100%) for ruling out TB.

Fig. 4 presents the algorithm for targeted diagnosis and treatment of LTBI and exclusion of active TB in household contacts aged ≥5 years and other at-risk populations.

Rationale for the recommendation on HIV-negative household contacts

The GDG noted the lack of any new data and agreed to continue use of the existing symptom-based algorithms (**Fig. 3**) for HIV-negative infants and children who are household contacts of TB cases. The GDG reiterated that active TB should be ruled out primarily by investigations, according to national guidelines. It noted that screening of child contacts could include LTBI testing and chest radiography, although the absence of those investigations should not pose a barrier for either diagnosis of active TB disease or provision of preventive treatment. In the absence of these tests, clinical assessment alone is sufficient to decide on eligibility for preventive treatment particularly for children < 5 years of age who are household contacts of a bacteriologically confirmed pulmonary TB.

Fig. 4   Algorithm for targeted diagnosis and treatment of LTBI and exclusion of active TB in HIV-negative household contacts aged ≥ 5 years and other at-risk populations
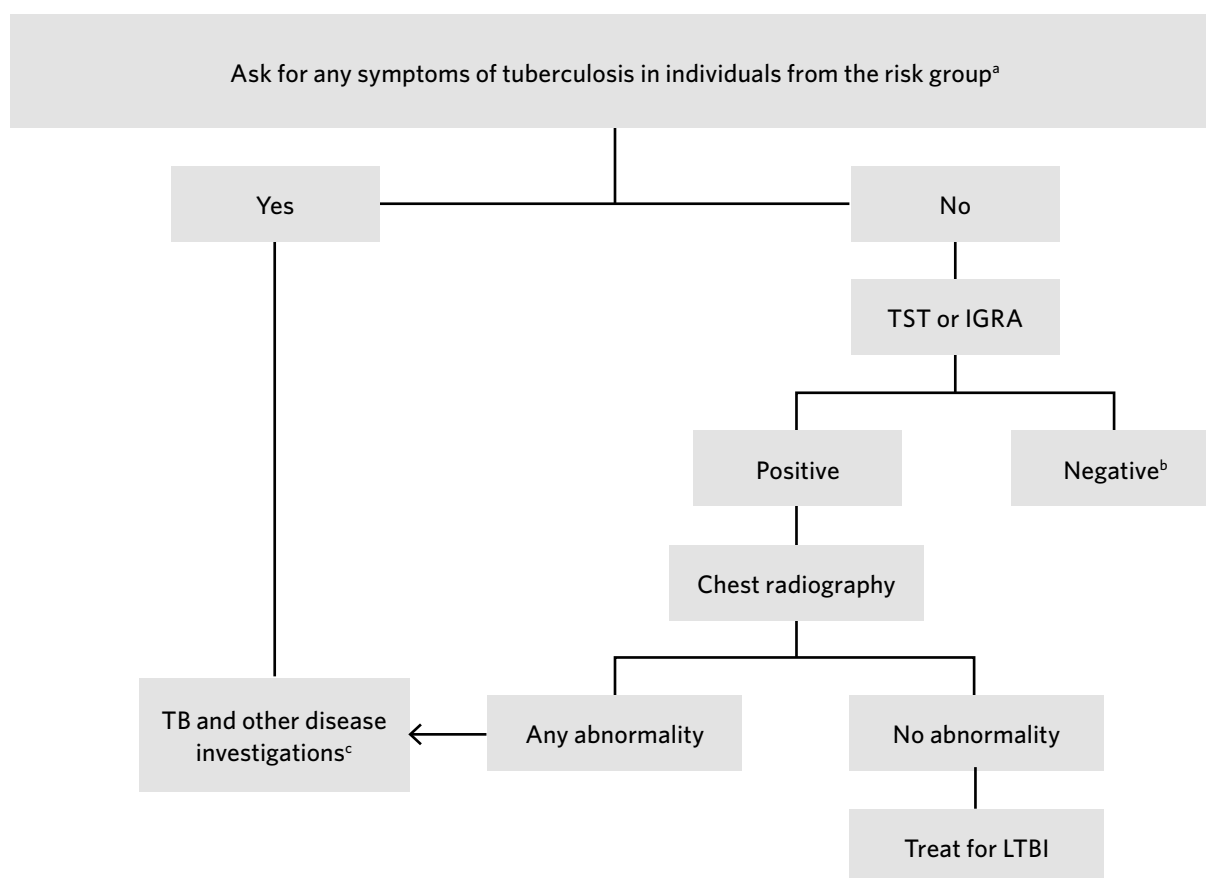
a   Any symptom of TB: cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue. An HIV test could be offered according to national or local guidelines or clinical judgement. Similarly, chest radiographs could be performed at this stage.

b   Clients for whom LTBI treatment is not indicated should be given information about TB, including the importance of seeking care if symptoms of TB develop.

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

The GDG also noted that symptom screening with or without the addition of chest radiography should be acceptable for individuals and programme managers. Chest radiography could increase the confidence of health care providers that active TB has been ruled out, thus reducing any concern about development of drug resistance; however, addition of chest radiography could incur costs for clients and inconvenience, as more clients would have to be investigated for TB and other diseases. The GDG noted the difficulty of assessing the preferences of children, which were not systematically documented.

3.3   Considerations for implementation

Addition of abnormal chest radiographic findings to the symptom screening rule would complicate logistics, increasing the cost, workload, infrastructure and availability of qualified staff. The GDG noted that chest radiography should not be a requirement or a barrier for initiating TB preventive treatment in people living with HIV because of the need for additional resources, in view of the marginal gain in negative predictive value.

People living with HIV who have any of the four symptoms or abnormal chest radiographic findings may have active TB and should be investigated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test. Other diseases that cause any of the four symptoms should be investigated in accordance with

national guidelines and sound clinical practice. People living with HIV who present any of the four symptoms but in whom active TB is excluded by investigations may be considered for preventive treatment.

The four-symptom screening method is recommended for all people living with HIV at every visit to a health facility or contact with a health worker. As combining chest radiography with symptom screening at every visit could represent a significant burden on the health system as well as on clients, it should be used only to exclude active TB before giving preventive treatment, with due respect for good clinical practice. The role of chest radiography in regular TB screening and its optimal frequency is uncertain. Local authorities should define its application and frequency on the basis of their local epidemiology, health infrastructure and resource availability.

It is critical to ensure proper follow-up and investigation for TB and other diseases in household contacts with abnormal chest radiographic findings or TB symptoms. The investigations should be performed in accordance with national guidelines and sound clinical practice. Contacts in whom active TB is excluded after investigations may be considered for preventive treatment.

Chest radiography and trained health care workers (e.g. radiologists) must be available to implement the screening rule. Where chest radiography is not available, absence of any TB symptoms alone may be considered as a criteria before preventive treatment. This would offer the highest sensitivity among symptom-based screening rules, and its negative predictive value is high in most settings.

4. Testing for latent tuberculosis infection

> - Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for LTBI. *(Strong recommendation, very low-quality evidence.* **New recommendation***)*
>
>   *Remark: The availability and affordability of the tests will determine which will be chosen by clinicians and programme managers. Neither TST nor IGRA can be used to diagnose active TB disease nor for diagnostic workup of adults suspected of having active TB.*
>
> - People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who have a negative LTBI test; LTBI testing can be used, where feasible, to identify such individuals. *(Strong recommendation, high-quality evidence. Existing recommendation)*
>
> - LTBI testing by TST or IGRA is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years. *(Strong recommendation, moderate-quality evidence. Updated recommendation)*
>
> Source of existing recommendation: Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva; World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Summary of evidence

There is no gold standard method for diagnosing LTBI. TST and IGRA require a competent immune response in order to identify people infected with TB and are imperfect tests for measuring progression to active disease.

A previous systematic review was updated to compare the predictive performance of IGRA and TST for identifying incident active TB in countries with a high TB incidence *(38)*. Only studies in which TST was compared with IGRA in the same population ("head-to-head" studies) were included. Relative risk ratios for TB for people who tested positive and those who tested negative with TST and IGRA were estimated. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**.

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 *(18, 39–42)*. The studies included people living 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 utility of the tests in specific at-risk populations.

Rationale for the recommendations

The evidence reviewed and the recommendations apply to the use of the two commercially available IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB) only. The GDG concluded that the comparison of TST and IGRA in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to active TB disease. The GDG noted that 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 reduce its use in scaling up programmatic management of LTBI.

The GDG also noted that equity and access could affect the choice and type of test used. The preferences of clients and programmes are, however, affected by several factors, such as the requirement for sophisticated laboratory infrastructure (e.g. for IGRA) and possible additional costs for clients (e.g. for travel) and programmes (e.g. for building and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages.

The GDG stressed that the global shortage of TST should be addressed urgently and called for more investment into research on novel tests for LTBI with better predictive value.

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 living with HIV. The GDG noted the importance of the tests for identifying recent conversion from a negative to a positive result, particularly among contacts of people with pulmonary TB, which is good practice for initiating TB preventive treatment. Nevertheless, recent studies among health care workers tested serially for LTBI in the USA showed that conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRA than with TST *(43)*. Thus, sound clinical judgement must be used in interpreting the results of these tests when used serially.

The GDG recommended that LTBI testing should not be a requirement for initiating TB preventive treatment for people living with HIV and child household contacts aged < 5 years, particularly in countries with a high TB incidence, given that clear benefits outweigh the risks. HIV-negative infant and child household contacts aged < 5 years and people living with HIV who have a negative LTBI test should be assessed case by case for their individual risk of exposure to TB and the added advantage of receiving preventive treatment.

Considerations for implementation

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

The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. Bacille Calmette-Guérin (BCG) vaccination plays a decisive role in reducing the specificity of TST, leading the choice towards IGRA-only strategies. The GDG noted, however, that the impact 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 is the case in most parts of the world, it has a variable, limited impact on TST specificity *(44)*. 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.

IGRAs are more costly and more technically complex to perform than the TST. Operational difficulties should be considered in deciding which test to use. For example, IGRA requires a phlebotomy, which can be difficult, particularly in very young children, laboratory infrastructure, technical expertise and expensive equipment; however, only a single visit is required to obtain a result (although patients may have to make a second visit to learn the result). TST 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.

5. Treatment options for latent tuberculosis infection

- Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. *(Strong recommendation, high-quality evidence. Existing recommendation)*

- Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence. **New recommendation**)*

- Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. *(Conditional recommendation, moderate-quality evidence. **New recommendation**)*

- The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone. *(Strong recommendation, moderate–high-quality evidence. Existing recommendation)*

Remark: Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on ART because of potential drug–drug interactions.

- In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of IPT, regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy. *(Conditional recommendation, low-quality evidence. Existing recommendation)*

Remark: People living with HIV in settings with high TB incidence and transmission, regardless of their TST status, obtain more benefit from IPT for ≥ 36 months than for 6 months. Those with a positive TST have a greater protective benefit and those receiving ART have a significant additional benefit from longer-term IPT. Use of TST is encouraged whenever feasible, but it is not a prerequisite for IPT. People with a negative TST should not receive 36 months of IPT. Settings with high TB incidence and transmission should be defined by national authorities, taking into consideration the local epidemiology and transmission of both TB and HIV.

Source of existing recommendations : Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015 (http://apps.who.int/medicinedocs/documents/s21682en/s21682en.pdf).

Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva; World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd Edition. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf).

Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings: 2015 update. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/174052/1/9789241508872_eng.pdf).

Summary of evidence

5.1   Daily isoniazid monotherapy

6 months' isoniazid monotherapy

Six months' daily monotherapy with isoniazid is the standard treatment for both adults and children living in countries with either high or low TB incidence. Several systematic reviews have demonstrated its preventive efficacy. A systematic review of RCTs involving people living with HIV *(17)* showed that isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51;0.87), and the preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22;0.61). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months' daily isoniazid monotherapy (RR 0.58; 95% CI 0.3;1.12) *(17)*. A recent 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, 0.65; 95% CI 0.50;0.83) *(45)*.

9 months' isoniazid monotherapy

No controlled clinical trials were found of 9 months' versus 6 months' isoniazid monotherapy. Re-analysis and modelling of the United States 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 *(46)*.

36 months' isoniazid monotherapy

A systematic review and meta-analysis of three RCTs of people living with HIV in settings with high TB prevalence and transmission showed that continuous IPT can reduce the risk for active TB by 38% more than 6 months' isoniazid *(47)*. The effect was greater in people with a positive TST (49% for active TB and 50% for death). In those with a negative TST, neither effect was significant, although the point estimate indicated a reduction in TB incidence of 27%.

5.2   Daily rifampicin plus isoniazid for 3–4 months

A systematic review *(48)* and its update in 2017 *(45)* showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid. The previous GDG therefore concluded that daily rifampicin plus isoniazid could be used as an alternative to isoniazid in settings with low TB incidence *(9, 10)*. We conducted a new review to compare the effectiveness in children of rifampicin plus isoniazid daily for 3 months with isoniazid for 6 or 9 months. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**. We identified one RCT and two observational studies *(49–51)*. The authors of the RCT *(50)* reported no clinical disease in either group and used new radiographic findings suggestive of active TB as a proxy for clinical disease. 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 two observational studies *(49, 51)*.

5.3   Daily rifampicin monotherapy for 3–4 months

A previous systematic review conducted for the 2015 LTBI guidelines *(48)*, updated in 2017 *(45)*, found similar efficacy for 3–4 months' daily rifampicin and 6 months of isoniazid (odds ratio, 0.78; 95% CI, 0.41;1.46). 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 (odds ratio, 0.03; 95% CI 0.00;0.48).

5.4 Weekly rifapentine plus isoniazid for 3 months

A new systematic review was conducted to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid with that of isoniazid monotherapy. The review covered four RCTs *(52–55)*, which were analysed for three subgroups: adults with HIV infection, adults without HIV infection and children and adolescents, who could not be stratified according to HIV status because the relevant studies were lacking. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**.

Two of the RCTs involved adults with HIV from South Africa, Peru and in a number of countries with a low incidence of TB. No significant difference was found in the incidence of active TB between participants given a 3-month weekly regimen of rifapentine plus isoniazid and 6 or 9 months of isoniazid monotherapy (RR 0.73, 95% CI 0.23;2.30). Furthermore, the risk for hepatotoxicity was significantly lower with the 3-month weekly regimen of rifapentine plus isoniazid in 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 weekly 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 a 3-month weekly regimen of rifapentine plus isoniazid and continuous isoniazid monotherapy in adults with HIV infection *(52)*. No significant difference in TB incidence was found in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB infection or death in participants given continuous isoniazid. In all the studies, the 3-month regimen of weekly rifapentine plus isoniazid was given under direct observation.

In a study of the 3-month weekly regimen of rifapentine plus isoniazid in 112 pregnant women, the rates of spontaneous abortion and birth defects were similar to those in the general US population *(56)*.

Table 2   Recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

Rationale for the recommendations

The selection of treatment options by programmes and clinicians should consider the characteristics of the clients who are to receive treatment to ensure that it is not only initiated but also completed. The GDG agreed that the benefits of all the treatment options outweigh the potential harm. They also noted that all the treatment options can be self-administered. An RCT showed that self-administered treatment of the 3-month regimen of weekly rifapentine plus isoniazid is not inferior to directly observed treatment *(57)*; however, there is little further evidence on self-administration of this regimen. The GDG noted that a requirement for a direct observation could be a significant barrier to the implementation. The GDG further noted that individuals receiving treatment, clinicians providing treatment and programme managers prefer shorter to longer regimens.

On the basis of existing practice, albeit, in the absence of a direct comparison, the GDG judged that 9 months' isoniazid is an equivalent option to 6 months of isoniazid in countries with a low TB incidence and a strong health infrastructure. It noted, however, that 6 months' isoniazid is preferable to 9 months from the point of view of feasibility, resource requirements and acceptability to patients.

The recommendation that people living with HIV should be given at least 36 months of daily isoniazid monotherapy is conditional, as continuous IPT depends on the epidemiology and transmission of TB, the health infrastructure and programme priorities.

The GDG agreed unanimously that the benefits of 3 months' daily rifampicin plus isoniazid for infants and children < 15 years of age outweigh the harm, given its safety profile, 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 quality of the evidence.

Considerations for implementation

Drug resistance and surveillance

There is no evidence of a significant association between bacterial resistance to TB drugs and use of isoniazid or rifamycins for the treatment of LTBI *(58, 59)*. Nonetheless, active TB disease must be excluded before TB preventive treatment is initiated (**section 3**), and regular follow-up is required to ensure early identification of people who develop active TB while receiving TB preventive treatment. National surveillance systems for resistance to TB drugs should be established in countries implementing programmatic management of LTBI.

Interactions with antiretroviral drugs

Regimens containing rifampicin and rifapentine should be prescribed with caution to people living with HIV who are on ART because of potential drug–drug interactions. These regimens should not be administered to people receiving protease inhibitors or nevirapine. The GDG noted that the 3-month regimen of weekly rifapentine plus isoniazid can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics *(60)*. Administration of rifapentine with raltegravir was found to be safe and well tolerated *(61)*. Rifapentine-containing regimens should not be administered with dolutegravir until more information becomes available. The GDG stressed the urgent need for studies of the pharmacokinetics of the 3-month regimen of weekly rifapentine plus isoniazid concomitantly with other drugs, particularly ART.

Monitoring of adverse events

As individuals who receive treatment for LTBI do not have active disease, their risk for adverse events during treatment must be minimized. Adverse reactions have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity), rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity). While most of these reactions are minor and occur rarely, specific attention should be paid to preventing drug-induced hepatotoxicity.

Individuals receiving treatment for LTBI should be monitored routinely at monthly visits to health care providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Patients receiving treatment should 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, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

There is insufficient evidence to support testing of baseline liver function *(62)*. It is, however, strongly encouraged, where feasible, for individuals with the following risk factors: history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks, and they should be tested

routinely 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).

Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive vitamin B6 supplements when taking isoniazid-containing regimens.

Adherence to and completion of preventive treatment

Adherence to the full course and completion of treatment are important determinants of clinical benefit to individuals and to the success of programmes. A systematic review conducted for the WHO 2015 LTBI guidelines *(9, 10)* provided heterogeneous results for interventions to improve treatment adherence and completion, and the evidence was considered inconclusive. The GDG noted that interventions to ensure adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. The WHO guidelines for treatment of drug-susceptible active TB propose several interventions to support adherence *(63)*, which could be applied to treatment of LTBI. Fixed-dose combinations such as co-trimoxazole plus isoniazid and isoniazid plus rifampicin should be used where possible to reduce the number of pills to be taken. Concerns about adherence should not be a barrier to use of preventive treatment.

6. Preventive treatment for contacts of patients with multidrug-resistant tuberculosis

> In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. *(Conditional recommendation, very low-quality evidence. **New recommendation**)*
>
> *Remarks*
>
> *The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.*
>
> *The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV).*
>
> *The drugs should be selected according to the drug susceptibility profile of the source case.*
>
> *Confirmation of infection with LTBI tests is required.*
>
> *This recommendation must not affect on-going placebo-controlled clinical trials of MDR-TB contacts on ethical grounds. The results of such clinical trials are crucial for updating this recommendation.*
>
> *Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.*

Summary of evidence

A systematic review of the effectiveness of preventive treatment for contacts of people with MDR-TB conducted for the 2015 LTBI guidelines *(9, 10)* was updated. The updated review comprised 10 studies (6 newly identified and 4 from the previous review) that allowed comparisons between participants who received preventive treatment for MDR-TB and those who did not. Because of clinical heterogeneity among the studies, a meta-analysis could not be performed. Of the 10 studies, one was excluded because only isoniazid monotherapy was used, and an additional five studies were excluded as fewer than 20 participants completed preventive TB treatment. Therefore, the quality of the evidence was based on only four studies. The evidence-to-decision and the GRADE tables are presented in **Annexes 1 and 2**.

No TB case was reported in either the intervention or the control group in one study *(64)*, while one case of active TB due to a drug-susceptible strain that was different from that of the source case was reported in another study *(65)*. The remaining two studies *(66, 67)* addressed the efficacy of preventive treatment. In one study of 119 cohorts, 104 contacts with LTBI initiated fluoroquinolone-based preventive treatment, of whom 93 (89%) completed treatment, and none developed active TB; while 3 of 15 (20%) contacts who refused treatment developed MDR-TB (odds ratio, 0.02, 95% CI 0.00;0.39) *(66)*. In the other study, confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored preventive treatment and in 13 of 64 (20.3%) children who did not receive proper preventive treatment (odds ratio, 0.2, 95% CI 0.04;0.94) *(67)*.

The drugs used in these studies were mainly fluoroquinolones (e.g. moxifloxacin, levofloxacin) with or without other agents (e.g. ethambutol, ethionamide). None of studies included a comparison of the risk for adverse events, although one reported that no serious adverse events could be attributed to fluoroquinolone-based preventive treatment *(66)*. The median proportion of participants who discontinued treatment because of adverse events in all the studies was 5.1% (interquartile range, 1.9–30.2%).

Rationale for the recommendations

Overall, the GDG judged that the potential benefits of targeted preventive treatment for MDR-TB contacts based on individual risk assessments outweigh the harm but acknowledged uncertainty about the efficacy of the intervention due to the lack of RCTs. It also noted that provision of preventive treatment for MDR-TB contacts would be acceptable, particularly to patients and health care workers. The GDG stressed that treatment should be given to selected individuals after a careful risk assessment, including intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the index case and potential adverse events. It should be given only to household contacts at high risk (e.g. children, people on immunosuppressive therapy and people living with HIV). Confirmation of infection by LTBI testing is required before individualized treatment is initiated.

Considerations for implementation

Close monitoring and treatment adherence

Close monitoring of adverse events and adherence to treatment is essential. The types of adverse events depend on the drugs used. Common adverse events associated with each drug are listed in the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (68). Adverse effects should be monitored according to the WHO framework for monitoring and managing the safety of drugs against active TB (69). The GDG reiterated that strict clinical observation and close monitoring for active TB disease based on sound clinical practice and national guidelines for at least 2 years is required, regardless of the provision of preventive treatment. Consideration should also be given to interactions with antiretroviral, immunosuppressant and other drugs when providing TB preventive treatment.

Informed consent

As the recommendation is based on very low-quality evidence, clients must be given detailed information about the benefits and harms of the preventive treatment and asked for explicit informed consent. In view of the uncertainty about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practice in similar situations.

Selection of drug regimen

The regimen of preventive treatment of MDR-TB contacts should be based on reliable information on the drug resistance profile of the source case. Later-generation fluoroquinolones (e.g. levofloxacin and moxifloxacin) are considered to be important components of a preventive treatment regimen unless the strain of the source case is resistant to them. Although there has been concern about the use of fluoroquinolones in children because retardation of cartilage development was shown in animals (70), similar effects have not been demonstrated in humans (68, 71, 72). There is limited evidence for the duration of treatment, and this should be based on clinical judgement. The regimens used in the studies conducted so far were given for 6, 9 and 12 months.

Resources and feasibility

For a programmatic approach, all the necessary resources should be in place, including for quality-assured testing for drug susceptibility, the necessary medications and a system for close monitoring of harm and adverse events. The feasibility of providing preventive treatment should be carefully assessed according to the availability of resources and the history and status of preventive treatment for drug-susceptible TB.

7. Issues in implementation

7.1 Ethical considerations

LTBI testing and treatment raise a range of ethical issues *(73, 74)*. First, LTBI is by definition an asymptomatic state. This alters the ethical obligations that would be imposed by active TB. For example, the absence of an immediate risk of transmission makes it unethical to restrict migration on the basis of the LTBI status of an individual. Secondly, the difficulty of accurate assessment of individual risk for the development of active TB poses a challenge to communication. Informed consent requires effective, adequate communication of the uncertainty in LTBI testing, the risk for development of active TB, possible side-effects of treatment and the protective benefits. Risk and uncertainty must be communicated in culturally and linguistically appropriate forms and feedback obtained after screening programmes. Thirdly, LTBI disproportionately affects individuals and groups that are already socially and medically vulnerable. Therefore, efforts must be made to ensure equity and human rights, so that the vulnerability of target groups does not preclude their access to screening and treatment. Any intervention for vulnerable groups should include minimization of the risk for stigmatization. Policies should be evaluated from an ethical perspective after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant *(75)*.

7.2 Programme management, monitoring and evaluation

National programmes should prepare a national plan for programmatic LTBI management, including prioritization of groups at high risk on the basis of local epidemiology and the characteristics of the health system. They 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 LTBI management. Furthermore, dedicated resources should be allocated, including for human resource development and service delivery in the community. National TB programmes should ensure meaningful engagement with affected populations, their communities, the private sector, other relevant health programmes and line ministries in both planning and implementing the interventions. The national TB programme is also encouraged to ensure access to comprehensive care for co-existing risk factors for TB, such as diabetes, undernutrition and tobacco smoking.

Preventive TB treatment for people living with HIV should be a core component of HIV preventive care and should be the responsibility of national AIDS programmes and HIV service providers. Preventive treatment should not be viewed as an isolated intervention but should be part of a comprehensive package of care.

Coverage of contact investigation and treatment of LTBI among child contacts and people living with HIV are among the top 10 core indicators for monitoring implementation of the End TB Strategy. Programmatic management of LTBI should include monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems *(76)*. Appropriate recording and reporting tools should be developed, and standardized indicators (**Table 3**) should be measured to regularly inform decision-making for programme implementation. Some may require changes to national legislation (e.g. making LTBI a notifiable condition) and to the policy framework, which should be addressed according to the local and national context. It is important to engage the private health sector and to ensure proper recording and reporting from both the private and public sectors. Use of electronic case-based monitoring will facilitate recording and reporting for LTBI management.

Table 3 Monitoring and evaluation indicators for programmatic management of LTBI recommended by WHO

	INDICATOR	NUMERATOR	DENOMINATOR	PURPOSE
CORE GLOBAL AND NATIONAL INDICATORS				
1	Proportion of children < 5 years who are household contacts of TB cases (according to national guidelines) who have completed investigations for TB	Total number of children < 5 years who were household contacts of TB cases who completed investigations for TB (according to national guidelines) during the reporting period	Total number of children < 5 years who are household contacts of TB cases (according to national guidelines) during the reporting period	Measures the capacity of the programme to ensure effective contact investigation, a key component of TB diagnosis and prevention among children < 5 years
2	Proportion of children < 5 years old who are household contacts of TB cases (according to national guidelines) who are eligible for TB preventive treatment who have started treatment	Total number of children < 5 years who are household contacts of TB cases who started TB preventive treatment during the reporting period	Total number of children < 5 years who are household contacts of TB cases who were eligible for TB preventive treatment during the reporting period	Measures the capacity of the programme to initiate treatment in children < 5 years who are household contacts and are eligible for TB preventive treatment
3	Proportion of eligible people living with HIV, newly enrolled in HIV care and started on TB preventive treatment	Total number of eligible people living with HIV who started TB preventive treatment during the reporting period	Total number of eligible people living with HIV and newly enrolled in HIV care during the reporting period	Measures the capacity of the programme to initiate treatment of all individuals in HIV care who are eligible for TB preventive treatment
CORE NATIONAL INDICATORS				
4	Proportion of eligible individuals in at-risk populations (as defined by national guidelines) tested for LTBI infection	Total number of individuals in at-risk populations who were tested for LTBI during the reporting period	Total number of individuals in at-risk populations who were eligible for testing during the reporting period	Measures coverage of testing at-risk populations eligible for TB preventive treatment
5	Proportion of individuals in at-risk populations (according to national guidelines) with a positive LTBI test who are eligible for TB preventive treatment and who have started treatment	Total number of individuals in at-risk populations who started TB preventive treatment during the reporting period	Total number of individuals in at-risk populations who have tested positive for LTBI and were eligible for TB preventive treatment during the reporting period	Measures the capacity of the programme to initiate treatment of individuals in at-risk populations who are eligible for TB preventive treatment
6	Proportion of eligible individuals in at-risk populations (according to national guidelines) with a positive LTBI test who started TB preventive treatment and completed the course	Number of individuals in at-risk populations who completed the course of TB preventive treatment during the reporting period	Total number of individuals in at-risk populations with a positive LTBI test who started TB preventive treatment during the reporting period	Measures the capacity of the programme to ensure that individuals in at-risk populations adhere to the full course of treatment
7	Proportion of eligible people living with HIV who completed a course of TB preventive treatment	Number of eligible people living with HIV who completed a course of TB preventive treatment during the reporting period	Total number of eligible people living with HIV who started TB preventive treatment during the reporting period	Measures the capacity of the programme to ensure that people living with HIV adhere to the full course of treatment
8	Proportion of children < 5 years who are household contacts of TB cases (according to national guidelines) who have completed a course of TB preventive treatment	Number of children < 5 years who are household contacts of TB cases (according to national guidelines) who completed a course of TB preventive treatment during the reporting period	Total number of children < 5 years who are household contacts of TB cases (according to national guidelines) who started TB preventive treatment during the reporting period	Measures the capacity of the programme to ensure that children < 5 years who are household contacts of TB cases adhere to the full course of treatment
OPTIONAL INDICATOR				
9	TB incidence rate in at-risk populations (as defined by national guidelines)	Total number of newly notified TB cases in at-risk populations during the reporting period	Total number of individuals in at-risk populations	Measures the impact of the programme on the incidence of TB in at-risk populations

From reference (12)

8. Research priorities

The review of the evidence for the recommendations exposed gaps in research that should be filled urgently, in addition to those identified during preparation of the 2015 guidelines.

8.1 Risks of at-risk populations for progression to active TB disease

Evidence on the risks of a number of at-risk populations for progression from LTBI to active disease will be crucial for determining the potential benefits of LTBI treatment and for designing appropriate public health interventions. In particular, strong evidence from clinical trials is lacking for the following groups: patients with diabetes, people with harmful use of alcohol, tobacco smokers, underweight people, people exposed to silica, patients receiving steroid treatment, patients with rheumatological conditions, indigenous populations and cancer patients. Both direct measurement of the incidence of active TB and methods for measuring the risk for active TB disease could be explored, such as use of genotyping to measure the risk for reactivation.

Evidence is also required on differential harm and the acceptability of testing and treatment for LTBI in specific risk groups, including socially adverse events such as stigmatization.

8.2 Defining the best algorithm for ruling out active TB

Operational and clinical studies should be conducted to exclude active TB before preventive treatment is given. The performance and feasibility of the algorithms proposed in these guidelines should be assessed. In particular, few data are available on children and pregnant women. Strategies to save cost and improve feasibility (e.g. use of mobile chest radiography) should also be explored.

8.3 Improved diagnostic tests and performance of LTBI tests in at-risk populations

Diagnostic tests with improved performance and predictive value for reactivation of TB are critically needed. In addition, the performance of LTBI tests should be evaluated in various at-risk populations, such as the best way of using the available tools (e.g. combination or sequential use of TST and IGRA) in each at-risk population.

8.4 Treatment options for LTBI

Research to find shorter, better-tolerated treatment regimens than those currently recommended is a priority. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people with alcohol use disorder and elderly people) are essential. In particular, there are no or very limited data on the use of rifapentine in children < 2 years and pregnant women. Studies should be conducted of the pharmacokinetics of interactions between rifamycin-containing regimens and other drugs, particularly antiretroviral drugs. In addition, the durability of protection by preventive treatment should be evaluated in settings in which TB is endemic, including the efficacy of repeated courses of preventive treatment.

8.5 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 at-risk population.

8.6   Risk of drug resistance following LTBI treatment

Programme-based surveillance systems and clinical studies are needed to monitor the risk for bacterial resistance to the drugs used in LTBI treatment. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data.

8.7   Adherence to and completion of treatment

Carefully designed studies, including RCTs, are required to generate evidence on the effectiveness of context-specific interventions for enhancing adherence and completion of treatment. The studies should include specific risk groups, depending on the available resources and the health system infrastructure. Use of "digital health" 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.

8.8   Cost–effectiveness

Although a number of studies of the cost-effectiveness of TB preventive treatment are available, their wide heterogeneity obviates a comprehensive appraisal of the cost-effectiveness of LTBI management stratified by population group and type of intervention. Direct measurement of cost-effectiveness in certain settings and populations would allow extension of the LTBI strategy at national or local level.

8.9   Preventive treatment for contacts of people with MDR-TB

RCTs with adequate power are urgently needed to update the recommendation on preventive treatment for contacts of people with MDR-TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as people living with HIV. The composition, dosage and duration of preventive treatment regimens for MDR-TB should be optimized, and the potential role of newer drugs with good sterilization properties should be investigated. The effectiveness and safety of preventive treatment for contacts of people with MDR-TB should be evaluated in operational conditions. Further evidence on the risk of contacts of people with MDR-TB for progression to active TB will be important for understanding the benefits of preventive treatment.

8.10   Programme management

Epidemiological research should be conducted to determine the burden of LTBI in various geographical settings and risk groups and as a basis for nationally and locally tailored interventions, including integrated community-based approaches. Research is also needed on service delivery models to ensure that patients are properly managed including the provision of additional interventions for tobacco smokers, illicit drug users, and people with harmful use of alcohol. Household implementation models could improve the effectiveness and efficiency of delivery of interventions. Tools should be developed and assessed to facilitate monitoring and evaluation of programmatic management of LTBI.

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Annex 1. GRADE profile tables for new recommendations

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

Prevalence and risk of LTBI in HIV-negative household contacts in 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 (1-14)	Cross-sectional	Not serious[1,2]	Serious[3]	Not serious	Not serious[4]	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[5]	Serious[6]	Not serious	Not serious[7]	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[8]	Serious[9]	Not serious	Not serious[10]	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[11]	Serious[12]	Not serious	Not serious[13]	13218/21962	1979/6763	2.04 (1.53;2.63)	293.9 (155.1;475.7)	Moderate	Important

1 Potential selection bias in (2), as only 69% of participants were household contacts.
2 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.
3 High heterogeneity among studies (I² = 94%) probably due to difference in background TB incidence. Risk ratios of two studies (1,5) showed opposite effect.
4 Small sample size in (5) (n < 50).
5 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.
6 High heterogeneity among studies (I² = 97%) probably due to the differences in background TB incidence. Risk ratio of one study (5) showed opposite effect.
7 Wide confidence interval of pooled risk ratio. Small sample sizes in (5) (n < 50) and (12) (n < 100).
8 Potential selection bias in (15), as only 89% of participants were household contacts.
9 High heterogeneity among studies (I² = 93%) probably due to differences in background TB incidence. Risk ratios in three studies showed opposite effects (5,19,21).
10 Small sample size in (5) and (18) (n < 50).
11 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.
12 High heterogeneity among studies (I² = 98%) probably due to differences in background TB incidence.
13 Small sample sizes in (5) and (26) (n < 100).

Development of active TB in household contacts with LTBI in high TB incidence countries

No. of studies	Quality assessment						No of contacts (active TB/no. LTBI)		Effect		Quality	Importance
	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[1]	Not serious	Serious[2]	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[3]	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.
1 Serious inconsistencies due to heterogeneity (I² = 71%): One study showed an increased risk in the age group 5–15 years. This was not observed in the other studies.
2 Small number of events.
3 High heterogeneity among studies probably due to differences in background TB incidence and methods used to diagnose active TB (I² = 89.3%).

Cumulative prevalence of active TB in household contacts irrespective of baseline LTBI status in high TB incidence countries

No. of studies	Quality assessment						No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
	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)[1]	Cohort	Not serious	Not serious	Serious[2]	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.
1 One outlier (28) was excluded because of uncertainty about the cases included (co-prevalent vs incident cases).
2 High heterogeneity among studies (I² = 87.6%), probably due to the difference in background TB incidence.

Active TB in household contacts with LTBI and in the general population in high-TB incidence countries (12 months)

ACTIVE TB DISEASE IN HOUSEHOLD CONTACTS WITH LTBI INFECTION IN HIGH TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 12 MONTHS)

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population[1]	RR (95% CI)	Absolute per 1000 (95% CI)	Quality	Importance
						No. of contacts (active TB/no. LTBI)		Effect			
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
2 (8,15)	Cohort	Serious[2]	Serious[3]	Not serious	Very serious[4]	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 (8)	Cohort	Serious[2]	Not serious	Not serious	Serious[6]	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 (8)	Cohort	Serious[2]	Not serious	Not serious	Serious[6]	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 (8,15)	Cohort	Serious[2]	Not serious[5]	Not serious	Serious[6]	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 (8)	Cohort	Serious[3]	Not serious	Not serious	Serious[6]	155/3879	13/10 000	30.74 (17.46;54.07)	38.7 (21.4;69)	Low	Critical

[1] LTBI does not apply to the general population.
[2] 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).
[3] High heterogeneity among studies (I² = 83.9%), probably due to differences in background TB incidence.
[4] Serious imprecision with a wide confidence interval for the effect estimates, probably due to small study size and number of outcome events.
[5] I² = 72.5%, indicating moderate heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.
[6] Few events and wide CI.

Active TB in household contacts with LTBI compared with general population in high-TB incidence countries (24 months)

ACTIVE TB DISEASE IN HOUSEHOLDS OF CONTACTS WITH LTBI INFECTION IN HIGH-TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP ≤24 MONTHS)[1]

No. of studies	Quality assessment					No of contacts (active TB/no. LTBI)		Effect		Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General pop[2]	RR (95% CI)	Absolute per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
3 (8,15,16)	Cohort	Serious[3]	Serious[4]	Not serious	Serious[5]	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[3]	Not serious	Not serious	Serious[5]	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[3]	Not serious	Not serious	Serious[5]	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[3]	Serious[6]	Not serious	Serious[5]	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[3]	Not serious[7]	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

1　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.

2　LTBI does not apply to the general population.

3　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.

4　High heterogeneity between studies probably due to difference in background TB incidence (I^2 = 84.4%).

5　Few events and wide CI.

6　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.

7　I^2 = 16%.

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

CUMULATIVE PREVALENCE OF ACTIVE TB IN HOUSEHOLD CONTACTS IRRESPECTIVE OF BASELINE LTBI STATUS IN HIGH TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 12 MONTHS)

No of studies	Quality assessment					No. of contacts (active TB/total)		Effect		Quality	Importance
	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[1]	Not serious[2]	Not serious	Serious[3]	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[1]	Not serious	Not serious	Serious[3]	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[1]	Not serious	Not serious	Serious[3]	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[1]	Not serious[2]	Not serious	Serious[3]	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[1]	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

1 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).
2 $I^2 = 0\%$.
3 Few events and wide CI.

Active TB in household contacts irrespective of LTBI status compared with general population in high-TB incidence countries (24 months)

CUMULATIVE PREVALENCE OF ACTIVE TB IN HOUSEHOLD CONTACTS IRRESPECTIVE OF BASELINE LTBI STATUS IN HIGH-TB INCIDENCE COUNTRIES COMPARISON WITH THE GENERAL POPULATION (FOLLOW-UP OF 24 MONTHS)[1]

No. of studies	Quality assessment					No of contacts (active TB/total no. contacts)		Effect		Quality	Importance
	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[2]	Not serious[3]	Not serious	Serious[4]	2/31 37/335 9/108 55/508 73/1791	55/10 000 100/10 000 82/10 000 41/10 000 26/10 000	14.8 (9.82;22.3)	83.9 (53.6;129.5)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 (8)	Cohort	Serious[2]	Not serious	Not serious	Serious[4]	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[2]	Not serious	Not serious	Serious[4]	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[2]	Serious[5]	Not serious	Not serious	8/102 5/439 16/161 10/691 80/2804	55/10 000 100/10 000 82/10 000 41/10 000 26/10 000	6.29 (2.88;13.72)	32.2 (11.4;77.4)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED OVER 15 YEARS VS GENERAL POPULATION											
3 (8,16,27)	Cohort	Serious[2]	Not serious[6]	Not serious	Not serious	34/432 49/719 301/9380	100/10000 41/10000 26/10000	11.67 (7.55;18.02)	59.4 (36.5;94.7)	Moderate	Important

1 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.
2 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.
3 Moderate heterogeneity among studies (I^2 = 67.1%) probably due to differences in background TB incidence.
4 Few events and wide CI.
5 High heterogeneity among studies (I^2 = 87.5%) probably due to differences in background TB incidence.
6 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 active TB in individuals with HIV on antiretroviral treatment (ART)?

Four-symptom screening plus chest radiographic findings to exclude active TB 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)								8 (7–9)	42 (35–46)	85 (70–93)	
False negatives (patients incorrectly classified as not having active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Serious[1]	None[2]	2 (1–3)	8 (4–15)	15 (7–30)	⊕⊕⊕◯ Moderate
True negatives (patients without active TB)								295 (260–327)	283 (250–314)	268 (237–297)	
False positives (patients incorrectly classified as having active TB)	2 studies 646 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	None[2]	695 (663–730)	667 (636–700)	632 (603–663)	⊕⊕⊕⊕ High

From references (29,30)

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

[2] 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 active TB in contacts of pulmonary TB cases without HIV in high TB incidence countries?

Chest radiographic findings for exclusion of active TB in contacts of TB cases 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 100 000	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[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	Sensitivity: 0.94 (95% CI: 0.86;0.98) Specificity: 0.87 (95% CI: 0.80;0.92) 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[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	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)

1 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).

2 Indirectness (see QUADAS-2): Some concern about applicability of reference standard in 2 studies – no downgrading.

3 Inconsistency: Little heterogeneity for sensitivity and specificity (based on visual inspection of CIs).

4 Imprecision: Precise estimates for sensitivity and specificity.

5 Publication bias: Not applicable (the evidence base for publication bias in studies of diagnostic test accuracy is very limited).

Any symptom for exclusion of active TB in contacts of TB cases 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 100 000	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Sensitivity: 0.73 (95% CI: 0.64;0.80) Specificity: 0.77 (95% CI: 0.61;0.87)	
True positives (patients with active TB)	11 studies 357 609 patients	Cross-sectional (cohort type accuracy study)	Very serious[1]	Not serious[2]	Not serious[3]	Not serious[4]	None[5]	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[1]	Not serious[2]	Serious[3]	Serious[4]	None[5]	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)

1   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) .
2   Indirectness (see QUADAS-2): No major concern about applicability.
3   Inconsistency: Moderate heterogeneity for sensitivity and significant heterogeneity for specificity (based on visual inspection of CIs) – downgrading on specificity.
4   Imprecision: Precise estimates for sensitivity and imprecise estimate for specificity.
5   Publication bias: Not applicable (the evidence base for assessing publication bias in studies of diagnostic test accuracy is very limited.

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

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

Head-to head-evaluations of TST and IGRA (N = 5)

Review question: Among people at high risk of LTBI 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. SR OUTCOME: PROGRESSION TO ACTIVE TUBERCULOSIS IN UNTREATED INDIVIDUALS										
5 (N = 7675 for TST, N = 7641 for IGRA) (44-48)	Prospectively followed cohorts	Serious (A1) (-1)	Serious TST: I² = 64.4% IGRA: I² = 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) I² = 64.4% IGRA RR = 2.03 (95% CI 1.18;3.50) I² = 49.6%	TST 10 more per 1000 (4 fewer to 37 more) IGRA 15 more per 1000 (3 more to 36 more)		Very low ⊕○○○	Critical
B. SR 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 pre- and post-delivery of ART Prospectively followed cohort of HIV-infected individuals	Serious (B1) (-1)	Serious TST: I² = 77.4% IGRA: I² = 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				Relative (pooled)	Effect	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision		Absolute effect	(GRADE)	

C. SR 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 more to 69 more) | Very low ⊕◯◯◯ | Critical |

D. SR 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. SR 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 more to 21 more) IGRA 10 more per 1000 (3 more to 22 more) | Very low ⊕◯◯◯ | Critical |

Notes on GRADE summary table

Overall quality:

All studies start with one point docked 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 will be 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 results is not expected to change the overall conclusions of this review.

A2: Serious unexplained inconsistency of RR estimate for TST. Points docked 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 are concerns with 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 definite 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

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	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)		
"RADIOLOGICAL" TB DISEASE: FOLLOW UP: RANGE 3–7 YEARS TO 7–11 YEARS; ASSESSED WITH: CHEST RADIOGRAPHY												
1 (49)	Randomised trial	Serious[1]	Not serious	Serious[2]	Not serious	None	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318;0.762)	122 fewer per 1000 (from 57 fewer 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[1,3]	Not serious	Serious[4]	Not serious	None	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197;0.559)	83 fewer per 1000 (from 55 fewer 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[5]	Not serious	Serious[4]	Serious[6]	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[7]	Not serious	Serious[4]	Not serious	None	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01;1.14)	60 more per 1000 (from 9 more to 121 more)	⊕⊕○○ Low	Critical

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	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)		
COMPLETION RATE: ASSESSED BY: COMPLETION OF > 80% OF TREATMENT WITHOUT INTERRUPTION OF > 2 MONTHS												
1 (51)	Observational study	Serious[5]	Not serious	Not serious	Serious[8]	None	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70;3.43)	389 more per 1000 (from 193 more to 671 more)	⊕○○○ Very low	Critical
DRUG-RESISTANT TB												
0									Cannot be estimated		–	Important

From references (49–51)

1 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.

2 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.

3 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.

4 No data compared with 6H. Downgraded by one level.

5 Risk of bias due to poor comparability of the two groups. Downgraded by one level.

6 Low event rate and wide 95% CI. Downgraded by one level.

7 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.

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

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

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

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	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 (52,53)	RCTs	Not serious	Not serious	Not serious[1]	Serious[2]	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 (52,53)	RCTs	Not serious	Not serious	Not serious[1]	Serious[2]	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 (52,53)	RCTs	Serious[3]	Not serious	Not serious[1]	Not serious	None	39/535 (7.3%)	59/513 (11.5%)	RR 0.627 (0.426;0.921)	43 fewer per 1000 (from 9 fewer to 66 fewer)	⊕⊕⊕◯ Moderate	Critical
HEPATOTOXICITY												
2 (52,53)	RCTs	Not serious[4]	Not serious	Not serious[1]	Not serious	None	8/535 (1.5%)	30/513 (5.8%)	RR 0.256 (0.118;0.553)	44 fewer per 1000 (from 26 fewer to 52 fewer)	⊕⊕⊕⊕ High	Critical

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	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)		
DRUG RESISTANT TB												
2 (52,53)	RCTs	Not serious	Not serious	Not serious[1]	Very serious[5]	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
COMPLETION RATE												
2 (52,53)	RCTs	Not serious	Not serious	Not serious[1]	Not serious	None	497/534 (93.1%)	397/520 (76.3%)	RR 1.255 (1.014;1.553)	195 more per 1000 (from 11 more to 422 more)	⊕⊕⊕⊕ High	Critical

1   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.
2   95% CIs of both relative and absolute effect include appreciable benefit and harm with 3HP.
3   Both trials were open-label, which may have introduced bias in ascertainment of adverse events.
4   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.
5   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 LTBI in adults without HIV

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

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		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 (54)	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179;1.074)	2 fewer per 1000 (from 0 fewer to 3 fewer)	⊕⊕⊕○ Moderate	Critical
ALL-CAUSE MORTALITY												
1 (54)	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	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 (54)	RCT	Serious[4]	Not serious	Serious[1]	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 (54)	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099;0.268)	23 fewer per 1000 (from 20 fewer to 25 fewer)	⊕⊕⊕○ Moderate	Critical
DRUG-RESISTANT TB												
1 (54)	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	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

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
COMPLETION RATE												
1 (54)	RCT	Not serious	Not serious	Serious[1]	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159;1.221)	131 more per 1000 (from 110 more to 153 more)	⊕⊕⊕◯ Moderate	Critical

[1] 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.

[2] 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.

[3] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.

[4] An open-label design of the trial may have introduced ascertainment bias.

[5] 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 LTBI in children and adolescents

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

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 (55)	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	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 (55)	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	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 (55)	RCT	Serious[4]	Not serious	Serious[1]	Not serious[3]	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 (55)	RCT	Not serious[5]	Not serious	Serious[1]	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 TUBERCULOSIS												
0									Cannot be estimated		-	Important

COMPLETION RATE

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
1 (55)	RCT	Not serious	Not serious	Serious[1]	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030;1.153)	72 more per 1000 (from 24 more to 124 more)	⊕⊕⊕◯ Moderate	Critical

[1] 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.

[2] 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.

[3] 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.

[4] An open-label design of the trial may have introduced ascertainment bias.

[5] 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 7: Should preventive treatment be recommended for contacts of patients with multidrug-resistant or rifampicin-resistant TB?

Preventive treatment for contacts of patients with multidrug- or rifampicin-resistant TB

Five studies that included fewer than 20 participants who completed preventive TB treatment were excluded. In addition, the study by Kristi was excluded as only isoniazid monotherapy was given.

Overall quality: very low

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB DISEASE (BOTH DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB)												
4 (56–59)	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04;0.94)[4]	154 fewer per 1000 (273 fewer to 36 fewer)	⊕○○○ Very low	Critical
							0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)		
							0/21 (0%)	0/10 (0%)	–[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	–[7]	0 more per 1000 (45 fewer to 45 more)		
INCIDENCE OF MDR-TB												
3[2] (56, 57, 59)	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)	⊕○○○ Very low	Critical
							0/21 (0%)	0/10 (0%)	–[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	–[7]	0 more per 1000 (45 fewer to 45 more)		

	Quality assessment						No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
MORTALITY												
0	No evidence								Cannot be estimated		-	Important
ADVERSE EVENTS												
0	No evidence								Cannot be estimated		-	Critical
DEVELOPMENT OF DRUG RESISTANCE												
0	No evidence											Important

1   Risk of bias in selection of the control group, and none of the studies adjusted for confounders. Downgraded by two levels.
2   The study by Shaaf et al. was excluded, as the incidence of MDR-TB was not reported.
3   Small sample sizes and wide 95% CIs. Downgraded by two levels.
4   Reference (58)
5   Reference (56)
6   Reference (57)
7   Reference (59)

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