WHO consolidated guidelines on tuberculosis

Module 1: Prevention

Tuberculosis preventive treatment

Second edition

World Health Organization

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

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

Evidence reviewers

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

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Recommendations for tuberculosis preventive treatment, 2020 update

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Evidence reviewers

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

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Abbreviations and acronyms

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

Definitions

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

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

Adolescent: is a person aged 10–19 years.

Adult: is a person aged > 19 years.

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

Child: is a person aged < 10 years.

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

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

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

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

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

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

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

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

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

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

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

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

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

Executive summary

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

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

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

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

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

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

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

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

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

1.3. Testing for TB infection

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

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

1.4. TB preventive treatment options

TB preventive treatment with isoniazid or rifamycins

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

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

TB preventive treatment with levofloxacin

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

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

Introduction

Background

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

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

Rationale

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

Scope of the current update

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

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

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

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

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

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

Target readership

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

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

1. Recommendations

1.1 Identifying populations for TB preventive treatment

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

People with HIV

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

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

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

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

Justification and evidence

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

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

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

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

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

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

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

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

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

Household contacts of people with TB, regardless of HIV status

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

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

Justification and evidence

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

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

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

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

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

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

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

Other people at risk

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

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

Justification and evidence

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

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

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

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

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

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

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

Implementation considerations

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

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

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

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

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

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

1.2 TB screening and ruling out TB disease

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

People with HIV

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

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

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

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

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

Justification and evidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Household contacts of a person with TB and other risk groups

Infants and children < 5 years of age[5]

Justification and evidence

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

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

Household contacts aged ≥ 5 years and other risk groups

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

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

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

Justification and evidence

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

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

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

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

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

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

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

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

The reference standard is culture.

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

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

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

Implementation considerations

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

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

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

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

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

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

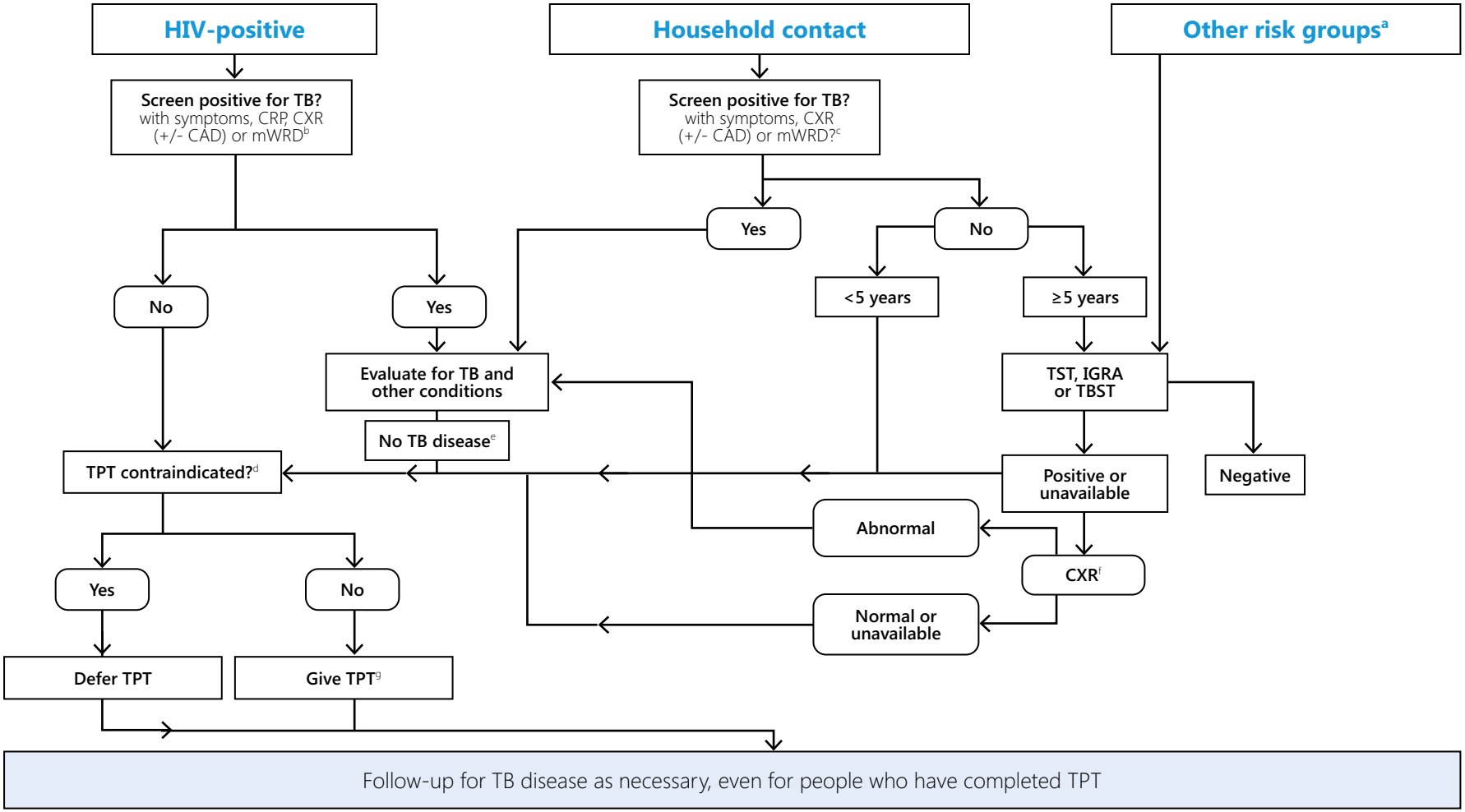
A previous history of TB or TPT should not be a contraindication for TPT in cases of re-exposure, after exclusion of reactivated disease. Such individuals, including those with fibrotic radiological lesions, may be at increased risk of progression *(65,66)*. The choice of TPT also depends on the presence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

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

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

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

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



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

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

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

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

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

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

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

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

1.3 Testing for TBI

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

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

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

Justification and evidence

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

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

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

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

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

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

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

Implementation considerations

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

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

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

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

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

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

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

1.4 TB preventive treatment options

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

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

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

TPT with isoniazid or rifamycins

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

Justification and evidence

Daily isoniazid monotherapy

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

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

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

Weekly rifapentine plus isoniazid for 3 months (3HP)

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

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

Daily rifampicin plus isoniazid for 3 months (3HR)

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

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

Daily rifapentine plus isoniazid for 1 month (1HP)

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

Daily rifampicin monotherapy for 4 months (4R)

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

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

Implementation and subgroup considerations

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

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

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

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

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

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

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

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

Drug–drug interactions

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

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

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

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

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

Pregnancy

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

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

Other subgroups and settings

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

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

Other considerations

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

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

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

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

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

TB preventive treatment with levofloxacin

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

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

Justification and evidence

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

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

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

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

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

Subgroup considerations

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

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

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

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

Implementation considerations

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

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

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

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

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

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

2. Monitoring and evaluation

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

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

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

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

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

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

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

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

3. Research gaps

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

Risks for progression to TB disease

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

Defining the best algorithm for screening and ruling out TB disease

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

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

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

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

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

TPT options

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

Monitoring of adverse events

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

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

Drug resistance and TPT

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

Adherence to and completion of treatment

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

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

Cost–effectiveness

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

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

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

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

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

Programme management

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

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

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

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

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

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

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

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

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

Annex 2. Methods and expert panels

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

A2.1 Scope and objectives

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

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

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

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

A2.2 Methods used to develop the guidelines

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

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

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

A2.3 Scoping and PICO question

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The recommendations are either strong or conditional.

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

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

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

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

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

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

A2.5 Publication, implementation, evaluation and expiry

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

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

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

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

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

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

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

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

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

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

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

A2.7 Declarations of interests and management of potential conflict

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

Guideline Development Group

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

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

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

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

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

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

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

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

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

External Review Group

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

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

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

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

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

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

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

Evidence reviewers

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

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

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

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

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Annex 3. GRADE summary of evidence tables

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

Contents

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

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

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

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

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

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

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

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

[b] Small number of events.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[c] Few events and wide CI.

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

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

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

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

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

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

Population: Adults and adolescents with HIV on ART

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

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

From references *(29,30)*

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

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

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

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

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

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

From references *(31–37)*

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

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

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

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

From references *(31–34,36,38–43)*

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

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

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

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

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

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

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

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

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

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

Notes on GRADE summary table

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

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

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

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

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

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

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

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

Overall quality: low

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

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

From references *(49–51)*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Explanations

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

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

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

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

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

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

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

[h] Unadjusted estimate.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[ac] Unadjusted absolute estimate.

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

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

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

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

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

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

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

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

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

Explanations

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

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

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

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

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

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

[g] The proportion of events among controls

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

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

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

[k] Small number of events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Bibliography: (see references *66 and 67*)

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

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

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

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Annex 4. GRADE evidence-to-decision tables

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

Contents

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

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

Background

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

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

Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of judgements

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

Conclusions

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

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

GRADE tables: SR1

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

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

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

SR2

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

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

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

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

[b] Few events.

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

SR3

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

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

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

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

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

Comparison with the general population for SR2

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

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

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

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

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

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

Comparison with the general population for SR3

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

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

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

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

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

[c] Few events and wide 95% CI.

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

Quality assessment						No. of contacts (active TB/total no. contacts)		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Comparator	General population	RR (95% CI)	Absolute risk per 1000 (95% CI)		
Comparison: Household contacts aged 0–5 years vs general population											
5 *(10,18,19,24,29)*	Cohort	Serious[b]	Not serious[c]	Not serious	Serious[d]	2/31	55/10 000	14.8 (9.82 ; 22.3)	83.9 (53.6 ; 129.5)	Low	Important
						37/335	100/10 000				
						9/108	82/10 000				
						55/508	41/10 000				
						73/1791	26/10 000				
Comparison: Household contacts aged 5–9 years vs general population											
1 *(10)*	Cohort	Serious[b]	Not serious	Not serious	Serious[d]	35/1464	26/10 000	9.2 (5.55 ; 15.23)	21.3 (11.8 ; 37)	Low	Important
Comparison: Household contacts aged 10–14 years vs general population											
1 *(10)*	Cohort	Serious[b]	Not serious	Not serious	Serious[d]	45/1340	26/10 000	12.92 (8.0 ; 20.86)	31 (18.2 ; 51.6)	Low	Important
Comparison: Household contacts aged 5–15 years vs general population											
5 *(10,18,19,24,29)*	Cohort	Serious[b]	Serious[e]	Not serious	Not serious	8/102	55/10 000	6.29 (2.88 ; 13.72)	32.2 (11.4 ; 77.4)	Low	Important
						5/439	100/10 000				
						16/161	82/10 000				
						10/691	41/10 000				
						80/2804	26/10 000				
Comparison: Household contacts aged > 15 years vs general population											
3 *(10,24,29)*	Cohort	Serious[b]	Not serious[f]	Not serious	Not serious	34/432	100/10 000	11.67 (7.55 ; 18.02)	59.4 (36.5 ; 94.7)	Moderate	Important
						49/719	41/10 000				
						301/9380	26/10 000				

[a] These comparisons were made in studies with a maximum follow-up of 24 months. The TB incidence in the general population was multiplied by a factor of 2 to estimate the number of cases occurring during 24 months.
[b] Ascertainment bias highly likely, because TB cases in the general population detected passively, while TB cases in the contacts detected actively. As a result, the relative and absolute risks might be overestimated. The composition of the general and study populations differs (general population of all ages versus a specific age group), and the TB incidence in the population was estimated by multiplying the yearly notification rate by a factor of 2.
[c] Moderate heterogeneity among studies (I^2 = 67.1%), probably due to differences in background TB incidence.
[d] Few events and wide 95% CI.
[e] High heterogeneity among studies (I^2 = 87.5%), probably due to differences in background TB incidence.
[f] Moderate heterogeneity among studies (I^2 = 72.5%), probably due to differences in background TB incidence.

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

Population:	People living with HIV (PLHIV) on ART	**Background** Active TB must be excluded before TPT is given. Since 2011, WHO has recommended use of a four-symptom screening rule – current cough, weight loss, night sweats and fever – to exclude active TB in PLHIV before initiating TPT. This policy has contributed to wider use of preventive treatment globally, with almost 1 million recipients in 2015. Since the recommendation was established in 2011, there has been a significant increase in coverage with ART, and recent studies have shown an additive effect of TPT and ART.
Intervention:	WHO-recommended four-symptom screening plus abnormal chest radiography (CXR). Positive symptom screening defined as presence of any of four symptoms; for adults and adolescents: cough of any duration, weight loss, night sweats or fever; for children: poor weight gain, fever, current cough or history of contact with a TB case.	
Role of the test:	Rule out active TB before giving preventive treatment.	
Linked treatments:	Screening negative → TPT.	
Anticipated outcomes:	True positive: Correct identification of an individual with active TB who should have further investigations. False negative: Incorrect identification of an individual with active TB as not having TB. True negative: Correct identification of an individual as not having active TB. False positive: Incorrect identification of an individual as requiring further investigations when they are actually TB negative.	
Setting:	High TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000).	
Perspective:	Health system and public health.	
Subgroups:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	TB is the most frequent cause of HIV/AIDS-related deaths worldwide, despite progress in access to ART. TB caused 0.4 million deaths among PLHIV in 2015, representing one third of all HIV-related mortality. TPT is one of the key collaborative activities against TB and HIV. Preventive treatment can reduce TB incidence by about 30% and by up to 60% among those with a positive TST. Active TB must be excluded before TPT is given.	
Test accuracy	How accurate is the test? ○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	We conducted a systematic review to assess the performance of the WHO-recommended four-symptom screening rule to exclude active TB before preventive treatment in HIV-positive people. Where possible, subgroup analyses were conducted by ART status, as the aim of this review was to study the effect with ART.	

Subgroup	Type of screening	No. of studies	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Negative predictive value for TB prevalence (%)			
					1	5	10	20
On ART	Symptom screening alone	7	51.0 (28.4;73.2)	70.7 (47.8;86.4)	99.3	96.5	92.8	85.2
	Symptom screening plus abnormal chest radiography	2	84.6 (69.7;92.9)	29.8 (26.3;33.6)	99.5	97.4	94.6	88.6
Not on ART	Symptom screening alone	15	89.3 (82.6;93.6)	27.2 (17.3;40.0)	99.6	98.0	95.8	91.1
	Symptom screening plus abnormal chest radiography	5	94.3 (76.2;98.8)	20.1 (7.6;43.8)	99.7	98.5	97.0	93.4
Pregnant women	Symptom screening alone	4	27.1 (16.3;41.7)	82.4 (79.1;85.2)	99.1	95.6	91.1	81.9
Children	Symptom screening alone	1	100 (76.8;100)	4.3 (1.8;8.7)	100	100	100	100

Two studies provided data on the combination of CXR and the four-symptom screening rule in PLHIV on ART. Any CXR abnormality was used in one study and CXR abnormality suggestive of TB in the other. Both studies showed increased sensitivity (from 60% to 88% and 53% to 80%) and decreased specificity (from 55% to 26% and 55% to 37%) with the addition of abnormal CXR. The pooled sensitivity in the studies of the combination of abnormal CXR plus the four-symptom screening rule (84.6%, 95% CI 69.7 ; 92.9) was higher than that with the symptom screening rule alone (52.2%, 95% CI 38.0 ; 66.0); however, specificity decreased (29.8%, 95% CI 26.3 ; 33.6 vs 55.5%, 95% CI 51.8 ; 59.2). The differences in sensitivity and specificity by screening type were both statistically significant.

Across studies, the median prevalence of TB among HIV-positive people on and not on ART was 1.5% (IQR: 0.6–3.5%) and 11.3% (IQR: 6.7–16.1%), respectively. When the prevalence of TB is 1.0%, the negative predictive value of the symptom screening rule is 99.3%, and addition of abnormal CXR increases it by 0.2%.

Judgement	Research evidence	Additional considerations
Balance of benefit vs harm	Do the benefits outweigh the harms? ● Yes ○ No ○ Equal ○ Uncertain	The anticipated desirable effect of screening is correct identification of PLHIV who do not have active TB and are thus eligible for TPT (true negatives). The other desirable effect is correct identification of those with TB who would be confirmed by subsequent investigations (true positives). The anticipated undesirable effect is incorrect classification of an individual with TB as not having TB (false negatives), as this would lead to inappropriate treatment of active TB by a preventive treatment regimen. In addition, individuals who screen positive would have to undergo further investigations for TB when they are actually TB negative (false positives).	By adding abnormal CXR, more patients would have to undergo investigations when they don't have TB. They might be lost to follow-up during investigations and miss an opportunity to be started on preventive treatment. Use of CXR could reduce concern of health workers about development of drug resistance.

Adults and adolescents on ART

Screening type	Test accuracy	Test results	Effect per 1000 individuals screened			Quality of evidence
			Prevalence 1%	Prevalence 5%	Prevalence 10%	
Symptom screening alone	Sensitivity (%): 51.0 (28.4;73.2) Specificity (%): 70.7 (47.8;86.4)	True positive	5 (3–7)	26 (14–37)	51 (28–73)	Low
		False negative	5 (3–7)	24 (13–36)	49 (27–72)	
		True negative	700 (473–855)	672 (454–821)	636 (430–778)	Low
		False positive	290 (135–517)	278 (129–496)	264 (122–470)	
Symptom screening plus abnormal chest radiography	Sensitivity (%): 84.6 (69.7;92.9) Specificity (%): 29.8 (26.3;33.6)	True positive	8 (7–9)	42 (35–46)	85 (70–93)	Moderate
		False negative	2 (1–3)	8 (4–15)	15 (7–30)	
		True negative	295 (260–327)	283 (250–314)	268 (237–297)	High
		False positive	695 (663–30)	667 (636–700)	632 (603–663)	

In the studies included in the review, the median prevalence of TB was 1.5% among PLHIV on ART. Accordingly, in a hypothetical population of 1000 PLHIV and at a TB prevalence of 1%, symptom screening alone would wrongly classify five TB patients as not having TB and being put on TPT, while symptom screening plus abnormal CXR would wrongly put only two TB patients on preventive treatment.

At a TB prevalence of 1%, symptom screening alone would require TB investigations for 58 extra non-TB patients for every TB case identified. Similarly, when symptom screening plus abnormal CXR were used, the number of HIV-positive people requiring TB investigations would increase (87 extra non-TB patients for every TB case identified).

	Judgement	Research evidence	Additional considerations
Evidence of accuracy	What is the overall certainty of the evidence of test accuracy? ○ Very low ● Low ○ Moderate ○ High ○ No included studies	A systematic review was conducted, which identified two cross-sectional studies of the WHO-recommended four-symptom screening rule plus abnormal CXR. The studies involved 646 participants, of whom 39 (6.0%) had active TB. The quality of the evidence for true positive–false negatives was considered moderate because of serious imprecision, while that for true negative–false negative was high. In view of the moderate quality of the evidence of true positive–false negatives and taking into account the small number of studies, the overall quality of the evidence was considered low.	
Management effects	What is the overall certainty of the evidence of effects of the management that is guided by the test results? ● Major uncertainty ○ Minor uncertainty	The studies included in the review were not designed to assess the effects of management with different screening strategies on patient outcomes (e.g. active TB incidence, mortality, drug resistance).	The efficacy of preventive treatment might depend on confirmation of TB infection in an LTBI test.
Values	Is there important uncertainty about or variation in how many people value the main outcomes? ● Important uncertainty or variation ○ No important uncertainty or variation		Addition of abnormal chest radiography increases burden on patients. Patients may value greater certainty in excluding active TB.
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements ○ Less resource requirements ○ Neither greater nor less ○ Varies ○ Don't know		More resources required, particularly if CXR is not available. Chest radiography would increase the number of HIV-positive people who undergo further investigations for TB.

	Judgement	Research evidence	Additional considerations
Cost effectiveness	Does the cost–effectiveness of the test favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies		Cost–effectiveness could vary by region and health system infrastructure.
Equity	What would be the impact on health equity? ○ Reduced ○ Increased ● Varies ○ Don't know		Impact on health equity depends on the setting (e.g. availability of CXR: could increase or decrease equity).
Acceptability	Is the test acceptable to key stakeholders? ○ No ○ Yes ● Varies ○ Don't know		Depends on availability of resources and infrastructure (e.g. electricity, radiologists).
Feasibility	Is the test feasible to implement? ○ No ○ Yes ● Varies ○ Don't know		Varies significantly, mainly by setting, health system infrastructure and workload of HIV clinics.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Test accuracy	**Very inaccurate**	**Inaccurate**	**Accurate**	**Very accurate**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of the evidence of test accuracy	**Very low**	**Low**	**Moderate**	**High**			**No studies**	
Certainty of the evidence of effects of management	**Major uncertainty**			**Minor uncertainty**				
Values	**Important uncertainty or variation**			**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Don't know**	
Cost-effectiveness	**Favours the comparison**		**Favours neither the intervention nor the comparison**		**Favours the intervention**	**Varies**	**No studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Don't know**	
Acceptability	**No**			**Yes**		**Varies**	**Don't know**	
Feasibility	**No**			**Yes**		**Varies**	**Don't know**	

Conclusions

What is the accuracy of WHO symptomatic screening plus abnormal chest radiography for excluding TB disease in individuals with HIV on antiretroviral treatment (ART)?

Type of recommendation	Symptom screening alone ☐	Symptom screening plus CXR ☒	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	Chest radiography may be offered to PLHIV and on ART and preventive treatment be given to those with no abnormal radiographic findings. *(Conditional recommendation, low-quality evidence)* *Remark: Chest radiography should not be a requirement for initiating preventive treatment.*		
Justification	Overall, the GDG agreed that the screening rule based on four symptoms is very useful for ruling out active TB before providing preventive treatment to PLHIV, regardless of whether they receive ART. It also noted the marginal potential benefits of adding abnormal CXR findings to the four-symptom screening rule. Moreover, increased use of CXR would pick up false-positives to the screening rule, so that more clients would be subjected to investigations for TB and other illnesses. Therefore, the GDG reiterated that CXR adds value only if it does not present a barrier for the provision of preventive treatment for PLHIV. The GDG also noted that symptom screening with or without abnormal CXR findings would be acceptable to individuals and programme managers. Furthermore, the use of CXR could enhance the confidence of health-care providers that active TB has been ruled out and reduce their concern about development of drug resistance. The addition of CXR may incur costs to clients as well as inconvenience, as more clients would have to be investigated for TB and other diseases.		
Subgroup considerations	Although no study was found of the additive role of CXR 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. 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.		
Implementation considerations	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 CXR should not be a requirement or a barrier for initiating TPT in PLHIV because of the need for additional resources, in view of the marginal gain in negative predictive value. PLHIV 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. PLHIV 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 PLHIV at every visit to a health facility or contact with a health worker. As combining CXR 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 CXR 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 essential to ensure the availability of CXR and trained health-care workers (e.g. radiologists) to implement the screening rule.		
Monitoring and evaluation			
Research priorities	• Performance and feasibility of the algorithms proposed in the present guidelines. • In particular, data on the screening rule for children and pregnant women.		

GRADE tables

Question: What is the performance of WHO-recommended four-symptom screening to exclude TB disease in individuals with HIV?

Population: Adults and adolescents with HIV on ART

Sensitivity	0.51 (95% CI: 0.28 ; 0.73)				
Specificity	0.71 (95% CI: 0.48 ; 0.86)	Prevalence	1%	5%	10%

Outcome	No. of studies; no. of patients	Study design	Factors that may decrease the quality of evidence					Effect per 1000 patients tested	Effect per 1000 patients tested	Effect per 1000 patients tested	Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	Pre-test probability of 5%	Pre-test probability of 10%	
True positives (patients with active TB)	7 studies; 4640 patients	Cross-sectional (cohort type)	Not serious	Not serious	Serious[a]	Serious[b]	None[c]	5 (3 ; 7)	26 (14 ; 37)	51 (28 ; 73)	Low
False negatives (patients incorrectly classified as not having active TB)								5 (3 ; 7)	24 (13 ; 36)	49 (27 ; 72)	
True negatives (patients without active TB)	7 studies; 4640 patients	Cross-sectional (cohort type)	Not serious	Not serious	Serious[a]	Serious[b]	None[c]	700 (473 ; 855)	672 (454 ; 821)	636 (430 ; 778)	Low
False positives (patients incorrectly classified as having active TB)								290 (135 ; 517)	278 (129 ; 496)	264 (122 ; 470)	

From references *31–37*

[a] Significant heterogeneity for sensitivity and specificity. Downgraded by 1.

[b] Wide confidence intervals. Downgraded by 1.

[c] Possibility of publication bias not excluded, but not considered of sufficient concern to downgrade.

Question: What is the performance of combination of CXR and WHO-recommended four-symptom screening to exclude TB disease in individuals with HIV?

Population: Adults and adolescents with HIV on ART

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

Outcome	No. of studies; no. of 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 of 1%	Pre-test probability of 5%	Pre-test probability of 10%	
True positives (patients with active TB)	2 studies; 646 patients	Cross-sectional (cohort type)	Not serious	Not serious	Not serious	Serious[a]	None[b]	8 (7 ; 9)	42 (35 ; 46)	85 (70 ; 93)	Moderate
False negatives (patients incorrectly classified as not having active TB)								2 (1 ; 3)	8 (4 ; 15)	15 (7 ; 30)	
True negatives (patients without active TB)	2 studies; 646 patients	Cross-sectional (cohort type)	Not serious	Not serious	Not serious	Not serious	None[b]	295 (260 ; 327)	283 (250 ; 314)	268 (237 ; 297)	High
False positives (patients incorrectly classified as having active TB)								695 (663 ; 730)	667 (636 ; 700)	632 (603 ; 663)	

From references *31 and 36*

[a] Imprecise estimate for sensitivity; downgraded by 1.

[b] Possibility of publication bias not excluded but not considered of sufficient concern to downgrade.

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

Population:	Contacts of pulmonary TB cases who are HIV-negative.	**Background** Active TB must be excluded before TPT is provided. WHO recommends use of the symptom screening rule alone for excluding active TB in children aged < 5 years who are contacts of TB cases. For contacts in other age groups, however, there is no clear guidance on methods for excluding active TB, as these groups were not targets for LTBI treatment in high TB incidence countries. In low TB incidence countries, WHO currently recommends the combination of any TB symptoms and any CXR abnormality for excluding active TB before preventive treatment.
Intervention:	Symptom screening and/or CXR.	
Role of the test:	Rule out active TB before providing preventive treatment.	
Linked treatments:	Screening negative →TPT.	
Anticipated outcomes:	True positive: Correct identification of an individual with active TB who should undergo further investigations. False negative: Incorrect identification of an individual with active TB as not having TB. True negative: Correct identification of an individual as not having active TB. False positive: Incorrect identification of an individual who should undergo further investigations who is actually TB negative.	
Setting:	High TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000).	
Perspective:	Health system and public health.	
Subgroups:	Children.	

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	Globally in 2015, there were an estimated 10.4 million incident TB cases and 1.8 million TB deaths. In order to end the global TB epidemic, management of LTBI is critical, as stated in the WHO End TB Strategy. Active TB must be excluded before providing TPT. A simple algorithm for excluding active TB is considered an essential component of programmatic LTBI management and could facilitate scaling-up of TPT.	
Test accuracy	How accurate is the test? ○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	We updated a systematic review conducted in 2012 to determine the sensitivity and specificity of symptoms and CXR screening for active pulmonary TB in HIV-negative people and those of unknown HIV status. To illustrate how different screening and diagnostic algorithms are expected to perform in ruling out active TB, a simple model was constructed to compare six screening methods. The main findings are summarized in the tables below:	

Performance of screening tools in a hypothetical population of 10 000 HIV-negative individuals at 2% TB prevalence

Algorithm	No. of studies	Sensitivity	Specificity	False negative at screening	Negative predictive value after negative screening	False positive at screening
Chest radiography: any abnormality	7	0.941	0.868	12	0.999	1294
Chest radiography: abnormality suggestive of TB	6	0.893	0.922	21	0.998	764
Any cough	10	0.627	0.775	75	0.990	2205
Cough ≥ 2–3 weeks	6	0.382	0.943	124	0.987	559
Any TB symptom	11	0.730	0.766	54	0.993	2303
Any TB symptom plus any chest radiography abnormality	[a]	1.00	0.701	0	1	2930

[a] No data could be obtained directly from the studies included in the systematic review; thus, the estimates were inferred from five studies of both CXR and symptom screening.

Judgement	Research evidence	Additional considerations

Performance of the screening tools in a hypothetical population of 10 000 HIV-negative individuals at 5% TB prevalence

Algorithm	No. of studies	Sensitivity	Specificity	False negative at screening	Negative predictive value after negative screening	False positive at screening
Chest radiography: any abnormality	7	0.941	0.868	30	0.996	1254
Chest radiography: abnormality suggestive of TB	6	0.893	0.922	54	0.994	741
Any cough	10	0.627	0.775	187	0.975	2136
Cough ≥ 2-3 weeks	6	0.382	0.943	309	0.967	542
Any TB symptom	11	0.730	0.766	135	0.982	2233
Any TB symptom plus any chest radiography abnormality	[a]	1.00	0.701	0	1	2841

[a] No data could be obtained from the studies included in the systematic review; thus, the estimates were inferred from five studies of both CXR and symptom screening.

The sensitivity and negative predictive value of CXR screening are high, especially if any CXR abnormality is used.
Symptom screening is less sensitive, resulting in a lower negative predictive value.
In several studies, it was assumed that people without CXR abnormalities and without a minimum set of symptoms did not have active TB and that a positive culture may be only transient or due to laboratory cross-contamination or subclinical TB. This is a standard design in TB prevalence surveys.
We identified only one study conducted among children < 5 years old (mean age, 19.2 months; standard deviation, 7.4). The sensitivity and specificity of abnormal CXR for TB (sensitivity, 55%, 95% CI 40 ; 70; specificity, 89%, 95% CI 87 ; 91) were higher than those of "persistent cough" (sensitivity, 45%, 95% CI 30 ; 60; specificity, 84%, 95% CI 82 ; 84). However, there was a high risk of selection bias, as the study included only children suspected of having TB from symptoms, contact history or known conversion to positive TST or IGRA.

	Judgement	Research evidence	Additional considerations
Balance of benefits vs harm	Do the benefits outweigh the harms? ● Yes ○ No ○ Equal ○ Uncertain	One anticipated desirable effect of screening is correct identification of individuals who do not have active TB and are thus eligible for TPT (true negatives). The other desirable effect is correct identification of those with TB that would be confirmed in subsequent investigations (true positives).The anticipated undesirable effect is incorrect classification of an individual with TB as not having TB (false negative), which would lead to inappropriate treatment of active TB by a preventive treatment regimen. In addition, individuals who screen positive have to undergo further investigations for TB when they are actually TB negative (false positive) and cannot be started on TPT immediately. In a hypothetical population of 10 000 individuals and at a TB prevalence of 2%, use of any TB symptoms alone would wrongly classify 54 TB patients as not having active TB and they would be given TPT. In contrast, use of any abnormal CXR finding would result wrongly in 12 TB patients being given preventive treatment. Use of the combination of any TB symptoms plus any CXR abnormal findings would result in no TB patients being given preventive treatment. At a TB prevalence of 2%, use of any TB symptoms alone would require TB investigations of 16 extra non-TB patients for every TB case identified, whereas use of any abnormal CXR finding would require TB investigations of 7 extra non-TB patients for every TB case identified. Use of the combination of any TB symptoms plus any CXR abnormal finding would increase the number of individuals requiring TB investigations to 15 extra non-TB patients for every TB case identified.	
Certainty of evidence of test accuracy	What is the overall certainty of the evidence of test accuracy? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence for any CXR abnormality was judged as low–moderate, while that for any TB symptoms was very low. Furthermore, there was no direct evidence on the combination of any CXR abnormality plus any TB symptoms. Therefore, the overall certainty of the evidence is considered very low.	

	Judgement	Research evidence	Additional considerations
Certainty of the evidence of management's effects	What is the overall certainty of the evidence of effects of management guided by test results? ● Major uncertainty ○ Minor uncertainty	The studies included were not designed to assess the effects of management with different screening strategies on patient outcomes (e.g. active TB incidence, mortality, drug resistance).	
Values	Is there important uncertainty about or variation in how much people value the main outcomes? ● Important uncertainty or variation ○ No important uncertainty or variation		Depends on health infrastructure and settings. Addition of abnormal CXR would increase burden on patients, although they might value an accurate test.
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements ○ Less resource requirements ○ Neither greater nor less ○ Varies ○ Don't know	A systematic literature review *(1)* was conducted for the previous LTBI guidelines, of studies published between 1981 and 2013 on the cost–benefit and cost–effectiveness of LTBI screening and treatment. In the 13 studies in which costs were expressed in US$, the cost of ruling out active TB in persons eligible for LTBI preventive treatment (including in most cases CXR, clinical evaluation and liver function tests) was US$ 28–188. Apart from a study conducted in India, the others were carried out in high-income and upper middle-income countries. Six studies on contacts of patients with active TB suggested that screening for and treatment of LTBI among contacts in general may save costs for the health care system and/or have a favourable incremental cost–effectiveness ratio. All the studies were conducted in low TB incidence countries. Cost–effective data for various screening methods or algorithms were not available.	

	Judgement	Research evidence	Additional considerations
Cost effectiveness	Does the cost–effectiveness of the test favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies		Depends on the setting. It may be cost–effective in the long term by preventing development of drug-resistant TB.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know		
Acceptability	Is the test acceptable to key stakeholders? ○ No ○ Yes ● Varies ○ Don't know		Depends on setting and availability of CXR.
Feasibility	Is the test feasible to implement? ○ No ○ Yes ● Varies ○ Don't know		Depends on setting and availability of CXR and human resources.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Test accuracy	**Very inaccurate**	**Inaccurate**	**Accurate**	**Very accurate**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of the evidence of test accuracy	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Certainty of the evidence of effects on management	**Major uncertainty**			**Minor uncertainty**				
Values	**Important uncertainty or variation**			**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Don't know**	
Cost–effectiveness	**Favours the comparison**		**Favours neither the intervention nor the comparison**		**Favours the intervention**	**Varies**	**No included studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Don't know**	
Acceptability	**No**			**Yes**		**Varies**	**Don't know**	
Feasibility	**No**			**Yes**		**Varies**	**Don't know**	

Conclusions

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

Type of recommendation	Any CXR abnormality ☐	CXR abnormality suggestive of TB ☐	Any cough ☐	Cough ≥ 2–3 week ☐	Any TB symptom ☐	Any TB symptom plus any CXR abnormality ☒	No recommendation ☐
Strength of recommendation	Strong ☐			Conditional ☒			
Recommendation	The absence of any symptoms and the absence of TB and 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)*						
Justification	Overall, the GDG agreed that the potential benefits of screening for active TB with the combination of any CXR abnormality plus any TB symptoms outweighs the harm because of the reliability of this screening rule for excluding active TB before providing preventive treatment. The GDG also noted that symptom screening with or without the addition of abnormal CXR would be acceptable for individuals and programme managers. Furthermore, the use of CXR could enhance the confidence of health care providers that active TB has been ruled out and reduce their concern about development of drug resistance. However, the addition of CXR may incur costs to clients as well as inconvenience, as more clients will be investigated for TB and other diseases.						
Subgroup considerations							
Implementation considerations	Contacts with abnormal CXR findings or TB symptoms must be followed up properly and investigated for TB and other diseases. Investigations should be performed in accordance with national guidelines and sound clinical practice. Contacts in whom active TB is excluded after investigations can be considered for preventive treatment. CXR and trained health care workers (e.g. radiologists) must be available to implement the screening rule. Where CXR is not available, contacts should be screened for any TB symptoms. This would offer the highest sensitivity among the symptom screening rules, and its negative predictive value would remain high in most settings.						
Monitoring and evaluation							
Research priorities	Evidence for the accuracy and feasibility of the recommended screening algorithm under programme conditions. Household models to improve the effectiveness and efficiency of intervention delivery. Studies of cost–effectiveness of screening rules. Strategies to save costs and improve feasibility (e.g. use of mobile CXR).						

GRADE tables

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

Index test: any abnormality in CXR| Reference test: Sputum culture and/or smear
Place of testing: Triage
Test–treatment pathway: CXR positive → confirmatory test (mycobacterial culture or GeneXpert) → anti-TB chemotherapy (6–9 months of antibiotics)

Outcome	No. of studies; no. of patients	Study design	Factors that may decrease quality of evidence					Effect per 100 000 Sensitivity: 0.94 (95% CI: 0.86 ; 0.98) Specificity: 0.87 (95% CI: 0.80 ; 0.92)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	7 studies; 251 410 patients	Cross-sectional (cohort type)	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%): 1882 (1716 ; 1954) Prevalence (5%): 4705 (4290 ; 4885)	Moderate
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%) : 118 (46 ; 284) Prevalence (5%): 295 (115 ; 710)	
True negatives (patients without active TB)	7 studies; 251 410 patients	Cross-sectional (cohort type)	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%) : 85 064 (78 106 ; 89 866) Prevalence (5%): 82 460 (75 715 ; 87 115)	Moderate
False positives (patients incorrectly classified as having active TB)								Prevalence (2%) : 12 936 (8134 ; 19 894) Prevalence (5%): 12 540 (7885 ; 19 285)	

Studies included: references *38,42,45,47–50*

[a] Limitations in study design (see QUADAS-2): High risk of selection bias in one study *(38)*. In all studies, less than half the participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture- and/or smear-negative (no active TB).
[b] Indirectness (see QUADAS-2): Some concern about applicability of reference standard in two studies. No downgrading.
[c] Inconsistency: Little heterogeneity in sensitivity or specificity (from visual inspection of 95% CIs).
[d] Imprecision: Precise estimates for sensitivity and specificity.
[e] Publication bias: Not applicable (the evidence for publication bias in studies of diagnostic test accuracy is very limited).

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

Index test: 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	No. of studies; no. of patients	Study design	Factors that may decrease quality of evidence					Effect per 100 000 Sensitivity: 0.73 (95% CI: 0.64 ; 0.80) Specificity: 0.77 (95% CI: 0.61 ; 0.87)	Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with active TB)	11 studies; 357 609 patients	Cross-sectional (cohort type)	Very serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None[e]	Prevalence (2%): 1460 (1282 ; 1608) Prevalence (5%): 3650 (3205 ; 4020)	Low
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%): 540 (392 ; 718) Prevalence (5%): 1350 (980 ; 1795)	
True negatives (patients without active TB)	11 studies; 357 609 patients	Cross-sectional (cohort type)	Very serious[a]	Not serious[b]	Serious[c]	Serious[d]	None[e]	Prevalence (2%): 74 970 (60 074 ; 85 260) Prevalence (5%): 72 675 (58 235 ; 82 650)	Very low
False positives (patients incorrectly classified as having active TB)								Prevalence (2%): 23 030 (12 740 ; 37 926) Prevalence (5%): 22 325 (12 350 ; 36 765)	

From references *38–48*

[a] Limitations in study design (see QUADAS-2): High risk of selection bias in one study *(38)* and unclear risk of bias for the reference standard in two studies. In 9 of the 11 studies, less than half the participants received the reference standard; accuracy was calculated under the assumption that those who did not receive the reference standard were culture- and/or smear-negative (no active TB).

[b] Indirectness (see QUADAS-2): no major concern for applicability.

[c] Inconsistency: moderate heterogeneity for sensitivity and significant heterogeneity for specificity (based on visual inspection of 95% CIs); downgrading on specificity.

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

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

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

Problem	Assess use of IGRA as an alternative to TST for identifying individuals at greatest risk of progression from LTBI to active TB in high TB incidence settings.	**Background** There is no gold standard for the diagnosis of LTBI. TST and IGRA indirectly identify TB infection by detecting memory T-cell response signifying the presence of host sensitization to *M. tuberculosis* antigens. They are generally deemed to be acceptable but imperfect tests. WHO currently recommends that IGRA should not replace TST in high TB incidence countries on the basis of a systematic review that showed similar performance in predicting development of active TB and its high cost and technical complexity. Either IGRA or TST can be used to test for LTBI in high-income and upper-middle-income countries with an estimated TB incidence < 100 per 100 000. Because of the global shortage of RT23 purified protein derivative, however, many countries are having difficulty in accessing it. The availability of an alternative test, IGRA, may facilitate scaling-up of programmatic LTBI management. Although sensitivity and specificity are usually used to evaluate the diagnostic accuracy of a test, there is no gold standard test for LTBI, and preventive treatment is meant to prevent the development of active TB. Therefore, the performance of tests for LTBI is better assessed from their predictive utility for development of active TB. The primary effect measure of interest is the relative risk ratio for TB among test-positives and test-negatives, which will be compared for TST and IGRA.
Option:	IGRA	
Comparison:	TST	
Main outcomes:	Incidence of active TB.	
Setting:	High TB incidence countries (estimated TB incident rate ≥ 100 per 100 000 population).	
Perspective:	Health system and public health.	

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	Currently, LTBI testing is not required before provision of preventive treatment in high TB incidence countries. It can identify individuals who would benefit most from LTBI treatment and is used in some high-incidence countries. Lack of availability of TST because of the global shortage of purified protein derivative has been cited as a barrier to scaling-up of programmatic management of LTBI. The availability of an alternative test, IGRA, may facilitate scaling-up.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Balance of effects</td><td>Do the benefits outweigh the harm?
● Yes
○ No
○ Equal
○ Uncertain</td><td>Five relevant studies of IGRA and TST in high TB incidence countries were identified (N = 7769). All were prospective cohort studies of participants who received both TST and IGRA. Two were conducted in India and three in South Africa. The populations studied were PLHIV, pregnant women, adolescents, health-care workers and household contacts. The RRs for test positives and test negatives were estimated for each test and pooled across studies. The pooled RR estimate was 1.49 for TST (95% CI 0.79 ; 2.80, 5 studies, I^2 = 64.4%) and 2.03 (95% CI 1.18 ; 3.50, 5 studies, I^2 = 49.6%) for IGRA. Although the pooled effect estimate for IGRA was slightly higher and the heterogeneity lower than for TST, the 95% CIs around the effect estimates overlapped and were imprecise.
<table><tr><th></th><th colspan="2">TST</th><th colspan="2">IGRA</th></tr><tr><th>Population</th><th>Pooled RR</th><th>I^2 (p value)</th><th>Pooled RR</th><th>I^2 (p value)</th></tr><tr><td>All populations (5 studies)</td><td>1.49 (0.79;2.80)</td><td>64.4% (0.024)</td><td>2.03 (1.18;3.50)</td><td>49.6% (0.094)</td></tr><tr><td>PLHIV (2 studies)</td><td>1.64 (0.24;11.18)</td><td>77.4% (0.035)</td><td>4.07 (0.18;92.72)</td><td>78.7% (0.030)</td></tr></table>There was little evidence for specific at-risk populations. Two studies were conducted in PLHIV, and the pooled estimates were imprecise.</td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td></td><td></td></tr>
<tr><td>Values</td><td>Is there important uncertainty about or variation in how much people value the main outcomes?
● Important uncertainty or variation
○ No important uncertainty or variation</td><td>No evidence retrieved.</td><td></td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know	A systematic review of studies of cost–effectiveness was conducted for the previous LTBI guidelines, which covered 39 studies published up to 2013. Cost inputs adjusted for currency and inflation varied widely among studies. The cost of a TST for detecting LTBI varied from US$ 1.3 in a study in Uganda to an average of US$ 31.5 in studies in the United Kingdom. Detection of LTBI with a IGRA test cost from US$ 22.5 in a study in Mexico to an average of US$ 97.1 in studies in the United Kingdom.	
Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ● Uncertain ○ Varies ○ No included studies	A systematic review *(50)* of 10 studies with a decision-analytical model for comparing the cost–effectiveness of IGRAs with that of TST in high-risk groups: child contacts, immunocompromised people and recent arrivals from high TB incidence countries. One study of child contacts was conducted in South Africa and the others in low TB incidence countries. The study in South Africa showed that providing preventive treatment without testing is most cost–effective among children aged 0–2 years. In children aged 3–5 years, an IGRA after a negative TST saved slightly more life-years, but saving one additional life year costed at least US$ 233 000. Six cost evaluations were conducted among immunocompromised people (including PLHIV) in Japan and the USA. Five studies showed that IGRA is more cost–effective than TST. In one study of patients taking immunosuppressive medicine, neither TST nor IGRA screening was more cost–effective than treatment without testing. These results depend on the performance of TST and IGRA assumed in the models, and the studies generally assumed higher sensitivity and/or specificity of IGRA for diagnosing LTBI. A systematic review conducted for the previous guidelines, which was updated in June 2017, covered five studies of TST and IGRA screening in adult contacts. None was conducted in high TB incidence countries. Two indicated that the TST alone was more cost–effective than IGRA alone; two found that IGRA was more cost–effective than TST alone but less cost–effective than sequential TST-IGRA. One study indicated that both strategies were better than no LTBI screening or treatment.	Very limited data from high TB incidence countries. Results of cost–effectiveness studies in low-incidence countries may not be generalizable to high-incidence countries.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know	No evidence retrieved.	The provision of more options generally increases equity; however, if the cost of the test is borne by patients, use of IGRA might be a greater barrier and might decrease equity.

	Judgement	Research evidence	Additional considerations
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Yes ● Varies ○ Don't know	No evidence retrieved.	Acceptability varies, particularly by resource availability. Although IGRA is likely to be largely acceptable to clinicians, its higher cost and requirement for sophisticated laboratory infrastructure may limit its acceptability to programmes. Both IGRA and TST have been used widely in many countries and are accepted.
Feasibility	Is the intervention feasible to implement? ○ No ○ Yes ● Varies ○ Don't know		Depends on the availability of resources and tests. IGRA: Phlebotomy is required, particularly for very young children, and sophisticated laboratory infrastructure, technical expertise and expensive equipment are required. TST: Can be performed in the field; training for intradermal injection, reading and interpretation are required, and there are frequent stock-outs due to global shortage. Both tests have been available for many years and are used widely in many countries.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or variation**			**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Don't know**	
Cost–effectiveness	**Favours the comparison**		**Favours neither the intervention nor the comparison**		**Favours the intervention**	**Uncertain**	**No included studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Don't know**	
Acceptability	**No**			**Yes**		**Varies**	**Don't know**	
Feasibility	**No**			**Yes**		**Varies**	**Don't know**	

Conclusions

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

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☒	Conditional ☐	
Recommendation	Either a TST or an IGRA can be used to test for LTBI. *(Strong recommendation, very low-quality evidence)* *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.*		
Justification	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 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 PLHIV. 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 TPT. 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. Thus, sound clinical judgement must be used in interpreting the results of these tests when used serially. The GDG recommended that LTBI testing not be a requirement for initiating TPT in PLHIV 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 PLHIV 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.		
Subgroup considerations			

Implementation considerations	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. 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. 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 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.
Monitoring and evaluation	
Research priorities	New tests with better predictivity for progression from LTBI to active TB disease than current tests. Predictive performance of both tests in various at-risk populations. Cost–effectiveness studies under different conditions of burden and subgroups (e.g. children, PLHIV).

GRADE table: Studies that included head-to-head evaluations of the TST and IGRA (N=5)

Review question: Among people at high risk of TB infection who are not treated with tuberculosis preventive therapy, which test (e.g. TST or IGRA) when positive, can best identify individuals most at risk of progression?

Systematic review outcome: The predictive utility of the TST vs. the commercial IGRAs for progression to active tuberculosis
Patients/population: Longitudinal studies of adults and children without active TB at baseline not given preventive therapy
Setting: Community cohorts, individuals attending outpatient clinics (e.g. HIV-positive people), individuals participating in RCTs, household contacts; all in high-incidence countries
Index test: TSR (RT23 purified protein derivative or purified protein derivative-S) and/or commercial blood-based IGRAs (QFT-GIT or T.SPOT.-TB)
Importance: Longitudinal studies on the predictive value of a positive IGRA in TB high-incidence countries (≥ 100/100 000) are still emerging. It is important to determine 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 for at least 1 year but can be either active or passive.

No. of studies (no. of individuals)	Design	Quality				Effect		Quality (GRADE)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect		
A. Systematic review outcome: Progression to active TB in untreated individuals									
5 (N = 7675 for TST, 7641 for IGRA) *(52–56)*	Prospective cohort	Serious risk of bias (A1) (-1)	Serious inconsistency (TST) I^2 = 64.4%, Serious inconsistency (IGRA) I^2 = 49.6% (A2) (-1)	Not serious (A3)	Serious imprecision (TST) No serious imprecision (IGRA) (A4) (-1)	TST RR = 1.49 (CI: 0.79 ; 2.80) I^2 = 64.4% IGRA RR = 2.03 (CI: 1.18 ; 3.50) I^2 = 49.6%	TST 10 more per 1000 (4 fewer to 37 more) IGRA 15 more per 1000 (3 to 36 more)	Very low	Critical
B. Systematic review outcome (subgroup analysis): Progression to active TB in immunocompromised people (includes HIV and other immunosuppressive conditions)									
2 (N = 725 for TST, 710 for IGRA) *(53,55)*	Prospective cohort of HIV-infected women pre- and post-delivery on ART Prospective cohort of HIV-infected individuals	Serious risk of bias (B1) (-1)	Serious inconsistency (TST) I^2 = 77.4% Serious inconsistency (IGRA) I^2 = 78.7% (B2) (-1)	Serious indirectness (B3) (-1)	Very serious imprecision for both TST and IGRA (B4) (-2)	TST RR = 1.64 (CI: 0.24 ; 11.18) IGRA RR = 4.07 (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

No. of studies (no. of individuals)	Design	Quality				Effect		Quality (GRADE)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect		
C. Systematic review outcome (subgroup analysis) : Progression to active TB among contacts of TB cases									
1 (N = 1511 for TST, 1498 for IGRA) *(56)*	Prospective cohort of household contacts	Serious risk of bias (C1) (-1)	Not assessed; single study (C2)	Serious Indirectness C3 (-1)	Serious imprecision C4 (-1)	TST RR, single study = 1.31 (CI: 0.85 ; 2.04) IGRA RR, single study = 1.87 (CI: 1.12 ; 3.11)	TST 14 more per 1000 (7 fewer to 45 more) IGRA 28 more per 1000 (4 to 69 more)	Very low	Critical
D. Systematic review outcome (subgroup analysis): Progression to active TB among TB health care workers									
1 (N = 195 for TST, 189 for IGRA) *(54)*	Prospective cohort of health-care workers	Serious risk of bias (D1) (-1)	Not assessed; single study (D2)	Serious Indirectness D3 (-1)	Very serious imprecision D4 (-2)	TST RR, single study = 0.40 (CI: 0.02 ; 9.81) IGRA RR, single study = 3.10 (CI: 0.13 ; 75.04)	TST 6 fewer per 1000 (9 fewer to 82 more) IGRA (difference cannot be computed)	Very low	Critical
E. Systematic review outcome (subgroup analysis): Progression to active TB among adolescents in a high-incidence setting									
1 (N = 5244 for both tests) *(52)*	Prospective cohort of adolescents	Serious risk of bias (E1) (-1)	Not assessed; single study (E2)	Serious Indirectness E3 (-1)	No serious imprecision E4	TST RR, single study = 2.71 (CI: 1.42 ; 5.15) IGRA RR, single study = 2.89 (CI: 1.55 ; 5.41)	TST 9 more per 1000 (2 to 21 more) IGRA 10 more per 1000 (3 to 22 more)	Very low	Critical

*Absolute risk: estimated by applying the RR estimate to the risk in the test negatives.

Notes to the GRADE summary table

Overall quality:
One point was removed from all the studies 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 scored high on a specific GRADE quality item.
Other study quality considerations: Newcastle–Ottawa scale quality items were considered when assessing the risk of bias. One point is removed if there is at least one concern.

A1: Risk of bias is possible, including selection bias, incorporation bias, ascertainment bias and publication bias. Methods for ascertaining TB included microbiological methods, but not all incident TB cases were confirmed definitively by culture. Publication bias not formally assessed but expected to be likely. Several large prospective studies are under way or unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
A2: Serious unexplained inconsistency of RR estimate for TST. Points removed for serious inconsistency in either estimate.
A3: Although few studies were included, they involved a range of populations, including adults and children, immunocompromised people and TB contacts, and provided direct evidence for these groups.
A4: Serious imprecision of RR estimate for TST. Lower limit of 95% CI indicates lack of predictivity. Points removed if serious imprecision was identified in either estimate.

B1: Risk of bias is possible, including selection bias, incorporation bias, ascertainment bias and publication bias. Incorporation bias could not be ruled out for the cohort of antepartum and postpartum women, because relevant information was not available; moreover, there was concern about selection. The reference standards used in the ART cohort study did not include index tests, and the assessors were not blinded to baseline TST results in patient records. Methods for ascertaining TB included microbiological methods, but not all incident TB cases were definitively diagnosed. Publication bias was not formally assessed but is expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
B2: Serious unexplained inconsistency of RR estimates for both TST and IGRA.
B3: This pooled estimate is based on only two studies: one on HIV-infected people on ART with a median CD4+ of approximately 250, and one on HIV-infected antepartum and postpartum women. No direct evidence for treatment of naive patients 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. The 95% CIs are wide and indicate both significant predictive performance and lack of predictivity. The studies had few events.

C1: Risk of bias is possible, including selection bias, incorporation bias (could not be assessed because of lack of information) and publication bias. Publication bias was not formally assessed but was expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
C2: Inconsistency not assessed.
C3: This single study comprised household case contacts in a high-incidence country. No direct evidence for other subpopulations of case contacts.
C4: TST effect estimates seriously imprecise. Lower limit of 95% CI indicates lack of predictivity.

D1: Risk of bias is possible, including selection bias, ascertainment bias (microbiological tests not used to diagnose TB), incorporation bias and publication bias. Publication bias was not formally assessed but was expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
D2: Inconsistency not assessed.
D3: This single study comprised health-care workers at a primary health-care clinic. No direct evidence for other subpopulations of health-care workers or all health-care settings.
D4: IGRA and TST effect estimates very seriously imprecise; 95% CIs are wide and indicate both significant predictive performance and lack of predictivity.

E1: Risk of bias is possible, including selection bias, ascertainment bias (inclusion of index tests in methods for ascertaining incident TB) and publication bias. Publication bias was not formally assessed but is expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
E2: Inconsistency not assessed.
E3: This single study comprised 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?

Problem	Children and adolescents < 15 years with LTBI and at high risk for active TB disease.	**Background** Treatment of LTBI can reduce the risk of reactivation by 60–90%. WHO currently recommends two approaches for the management of LTBI, based on TB incidence and income. For high TB incidence countries, WHO recommends isoniazid preventive therapy for PLHIV and children aged < 5 years who are household contacts of people with TB. The recent WHO guidelines provide several treatment options for use in high- or upper-middle-income countries with low TB incidence. A previous systematic review suggested that the efficacy of a 3-month regimen of daily rifampicin plus isoniazid is similar to that of daily isoniazid regimens.
Option:	3 months' daily rifampicin + isoniazid (3RH).	
Comparison:	6 or 9 months' isoniazid monotherapy.	
Main outcomes:	Incidence of active TB, mortality, adverse events, treatment completion rate, drug-resistant TB.	
Setting:	High TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000).	
Perspective:	Health system and public health.	

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	Uptake of LTBI treatment is still suboptimal: only 38% of PLHIV were newly enrolled in care in 2015 and 7.1% of child household contacts < 5 years started on preventive treatment. A systematic review *(57)* showed that failure to complete treatment accounts for a large loss in the cascade of care for LTBI management. Shorter regimens may improve completion rate and facilitate scaling-up of LTBI treatment in high TB incidence countries.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Balance of effects</td><td>Does the benefit outweigh the harm?
● Yes
○ No
○ Uncertain
○ Equal</td><td>
<table>
<tr><th>Outcome</th><th>3–4RH</th><th>6H/9H</th><th>Relative effect (RR) (95% CI)</th><th>Difference (95% CI)</th></tr>
<tr><td>Incidence of active TB (1 RCT)</td><td>26/220 (11.8%)</td><td>48/200 (24.0%)</td><td>RR 0.492 (0.318–0.762)</td><td>122 fewer per 1000 (from 57 to 164 fewer)</td></tr>
<tr><td>Adverse events (1 RCT)</td><td>27/650 (4.2%)</td><td>25/200 (12.5%)</td><td>RR 0.332 (0.197–0.559)</td><td>83 fewer per 1000 (from 55 to 100 fewer)</td></tr>
<tr><td>Adverse events (1 observational study)</td><td>1/220 (0.5%)</td><td>5/264 (1.9%)</td><td>RR 0.24 (0.03–2.04)</td><td>14 fewer per 1000 (from 18 fewer to 20 more)</td></tr>
<tr><td>Completion rate (1 RCT)</td><td>220/238 (92.4%)</td><td>200/232 (86.2%)</td><td>RR 1.07 (1.01–1.14)</td><td>60 more per 1000 (from 9 to 121 more)</td></tr>
<tr><td>Completion rate (1 observational study)</td><td>48/72 (66.7%)</td><td>29/105 (27.6%)</td><td>RR 2.41 (1.70–3.43)</td><td>389 more per 1000 (from 193 to 671 more)</td></tr>
</table>
A systematic review included one RCT and two observational studies. In the RCT, no cases of clinical TB disease were reported. Significantly fewer children given 4RH than those given 9H developed new radiographic abnormalities suggestive of TB. In the same study, higher treatment adherence rate and fewer adverse events were observed in children given 3 or 4RH than in those given 9H.
</td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
● Low
○ Moderate
○ High
○ No included studies</td><td></td><td>Although the quality of the evidence was low, data on adult populations support the benefits of 3RH.</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about or variation in how much people value the main outcomes?
○ Important uncertainty or variation
● No important uncertainty or variation</td><td>We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (1). Data were available from 142 respondents, of whom 59 had at least one child. The respondents were asked to rate the importance of each attribute of the LTBI treatment regimen on a five-point scale on which 5 is “very important” and 1 is “not important”. 90–100% of the respondents with children rated the following attributes as “very important” or “important” for their children: shorter duration, fewer side-effects, fewer visits to the clinic, easy to swallow and less frequent intake. Fewer respondents (78.0%) rated “no need for direct observed therapy (DOT)” as “very important” or “important”.</td><td></td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Greater resource requirements with the intervention ● Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know	No evidence retrieved.	Treatment is shorter with 3RH than 6H/9H. Use of 3RH would require fewer resources, particularly because the drug combination is already being used for treatment of active TB.
Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies	No evidence retrieved.	Fewer resources required with 3RH, while its effectiveness is greater because of higher completion rate and safer profile. Cost–effectiveness favours 3RH in studies in adult populations.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know	No evidence retrieved.	The availability of more options would increase equity in accessing health services.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ● Yes ○ Varies ○ Don't know	No evidence retrieved.	

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ● Yes ○ Varies ○ Don't know	Co-administration of rifampicin with protease inhibitors is not recommended. Rifampicin is known to significantly lower plasma concentrations of dolutegravir, and the dosing schedule might have to be increased to to twice daily, but there are very few studies and limited clinical experience with this combination *(67)*.	Drug interactions preclude its co-administration with protease inhibitors or nevirapine (e.g. infants born to HIV-positive mothers receiving nevirapine). Little concern about drug interactions in HIV-negative child contacts.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or variation**			**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Don't know**	
Cost–effectiveness	**Favours the comparison**		**Favours neither the intervention or the comparison**		**Favours the intervention**	**Varies**	**No included studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Don't know**	
Acceptability	**No**			**Yes**		**Varies**	**Don't know**	
Feasibility	**No**			**Yes**		**Varies**	**Don't know**	

Conclusions

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

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☒	Conditional ☐	
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)*		
Justification	The GDG unanimously agreed that the benefits of 3RH outweigh the harm, given its safer profile, higher completion rate than with isoniazid monotherapy and the availability of child-friendly fixed-dose combinations of rifampicin and isoniazid. The GDG noted that, although the quality of the evidence was low, data on adult populations also support the benefits of 3RH. A systematic review of RCTs on preventive treatment options conducted in 2014 showed that the efficacy and the risk for hepatotoxicity are similar for 3RH and isoniazid monotherapy. The GDG noted that use of 3RH would require fewer resources, given the shorter duration of treatment, which would reduce the number of clinic visits required. It also suggested that the initial cost of use of 3RH would be low, as it is already being used for treatment of active TB. The GDG agreed that cost–effectiveness favours 3RH because of the higher completion rate, safer profile and fewer resources required. The GDG also noted that, although direct evidence for the cost–effectiveness of 3RH in children is limited, the cost–effectiveness of shorter preventive treatment including 3RH is supported by a body of evidence in adult populations. The GDG agreed that there is no important uncertainty or variation in clients' values and preferences. It also agreed that the acceptability of 3RH is high, given its shorter duration and long use by health-care workers for treatment of active TB disease.		
Subgroup considerations			
Implementation considerations	The GDG strongly encouraged use of paediatric fixed-dose combinations of rifampicin and isoniazid for children, as they will increase acceptability and feasibility. It also noted that 3RH should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions; the regimen cannot be co-administered with protease inhibitors or nevirapine. The GDG further emphasized the importance of surveillance systems for rifampicin-resistance TB.		
Monitoring and evaluation			
Research priorities	Further research on reliable methods for excluding active TB among children.		

GRADE table

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

Overall quality: low

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin + isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
"Radiological" TB disease: *(59)* (follow up: 3–7 years to 7–11 years; assessed with: CXR)												
1	RCT	Serious[a]	Not serious	Serious[b]	Not serious	None	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318–0.762)	122 fewer per 1000 (from 57 to 164 fewer)	Low	Critical
Mortality												
0									Cannot be estimated		–	Important
Adverse events: *(59)* (follow up: 3–7 years to 7–11 years; assessed by recognition of symptoms and elevated liver enzymes)												
1	RCT	Very serious[a,c]	Not serious	Serious[d]	Not serious	None	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197–0.559)	83 fewer per 1000 (from 55 to 100 fewer)	Very low	Critical
Adverse events: *(60)* (follow up: median 97–197 days; assessed with: liver toxicity test and clinical)												
1	Observational	Serious[e]	Not serious	Serious[d]	Serious[f]	None	1/220 (0.5%)	5/264 (1.9%)	RR 0.24 (0.03–2.04)	14 fewer per 1000 (from 18 fewer to 20 more)	Very low	Critical
Completion rate: *(59)* (follow up: 3–7 years to 7–11 years)[i]												
1	RCT	Serious[g]	Not serious	Serious[d]	Not serious	None	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01–1.14)	60 more per 1000 (from 9 to 121 more)	Low	Critical

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin + isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
Completion rate: *(61)* (assessed from: completing > 80% of treatment without interruption of > 2 months)												
1	Observational studies	Serious[e]	Not serious	Not serious	Serious[h]	None	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70–3.43)	389 more per 1000 (from 193 to 671 more)	Very low	Critical
Drug-resistant TB												
0									Cannot be estimated		–	Important

From references *59–61*

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

[b] There was no clinical disease. The outcome reported was new radiography findings suggestive of possible active disease. No comparison with 6H. Downgraded by one level.

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

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

[e] Risk of bias because of non-comparability of the two groups. Downgraded by one level.

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

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

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

[i] Adherence rates reported; compliance considered poor if no medication was detected in urine strips, if patients did not return for follow-up visits or if they were lost to follow-up. Poor compliance was considered non-completion in the analysis.

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

Population:	People of all ages at risk of active TB *in high TB burden settings*
Intervention:	A regimen with 4 months of daily rifampicin (4R)
Comparison:	Another regimen (9-months of isoniazid alone [9H] in the studies identified and reviewed)
Main outcomes:	Outcomes scored as critical or important by the GDG were: active TB incidence, mortality, adverse events, treatment completion, emergence of drug resistance
Setting:	For this PICO question the GDG considered data from two phase 3 randomized controlled trials (RCTs) of the 4R regimen published in 2018 that included sites in high TB burden settings, as well as earlier phase 1 and phase 2 studies coordinated by the same investigators *(62–65)*. The 4R regimen had already been recommended by WHO for low TB incidence settings by the time the results of the phase 3 trials in children and adults were released in 2018 from previous evidence. Phase 2 *(64)* and phase 3 *(62,63)* open-label RCTs were conducted in nine countries (Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Republic of Korea and Saudi Arabia), assigning children (0–17 years) and adults (≥18 years) with LTBI to receive treatment with 4R or 9H. A documented positive TST was an enrolment criterion for children; children < 5 years with negative TST and household exposure to TB were also included. Eligibility of adults was determined by positive TST or IGRA; study criteria for an increased risk of progression to active TB and if their provider recommended treatment with isoniazid. In children, the outcomes were adverse events of grades 1–5 that resulted in permanent discontinuation of a trial medicine (primary outcome), as well as treatment adherence, adverse event profile, and microbiologically confirmed active TB during 16 months of follow-up after randomization (secondary). In adults, the primary outcome in the phase 2 trial was incidence of grades 3–5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active TB within 28 months of randomization. The primary outcome of the adult phase 3 trial was microbiologically confirmed active TB within 28 months of randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active TB, grades 3–5 adverse events, and treatment completion. The outcomes extracted from the trial to address those in the PICO were the following (see also the GRADE evidence summary table for PICO 6 in Annex 3): Incidence of active TB (in all forms) in adults; incidence of active TB (microbiologically confirmed) in adults; mortality (all cause) of adults during treatment; mortality (related to drug) of adults during treatment; adverse events (grades 3–5) in adults; adverse events (related grades 3–5) in adults; treatment completion (ever) in adults; incidence of active TB (all forms) in paediatrics; incidence of active TB (microbiologically confirmed) in children; mortality (all causes) of children during treatment; mortality (related to drug) of children during treatment; adverse events (grades 3–5) in children; adverse events (related grades 3–5) in children; treatment completion (ever) in children; incidence of active TB (microbiologically confirmed) in HIV-positive adults; incidence of active TB (all forms) in HIV-positive adults; adverse events (grades 3–5) in HIV-positive adults; adverse events (related grades 3–5) in HIV-positive adults. No attempt was made to extract outcomes for emergence of resistance given the incompleteness of the data (for the eight adults with confirmed active TB in the phase 3 trial, drug-susceptibility test results were not available for four, and two were susceptible to all the drugs tested. Of the other two, one was resistant to isoniazid detected 8 weeks after starting 9H, and one was resistant to rifampicin 2 months after completing 4R. The drug susceptibility of the putative source case was not available). The GDG decided to downgrade the risk of bias by one level to serious because of the open-label design of the trials, possibly leading to performance bias. The risk of detection bias was mitigated by a blinded expert adjudication of active TB and adverse events by a three-member, independent review panel; assessment of treatment completion was based on pill counts at routine follow-up visits. There were 18 per protocol exclusions among those randomized to 9H and 19 per protocol exclusions among those randomized to 4R. These exclusions were due to household contact with isoniazid or rifampicin-resistant TB (post-randomization). Nine individuals randomized to 9H and five individuals to 4R withdrew their consent post-randomization. The GDG noted that Inconsistency could not be judged given that there was only a single trial and replication of findings by other studies would be desirable. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 4R with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TPT. Some study sites were low TB incidence settings for which a WHO recommendation for use of 4R already exists. As a result, the certainty of the estimates of effect (quality of evidence) was moderate for the incidence of active TB, mortality, adverse events and treatment completion in both adults and children. The quality was low for all outcomes in HIV-positive adults because of additional downgrading due to imprecision (small numbers of observations in this sub-group which was not stratified at randomization) *(62–65)*.
Perspective:	The PICO question and GDG discussion addressed the expected performance of the regimen in high TB burden settings, given that a WHO recommendation for use of 4R in low TB burden settings already exists based upon the evidence reviews conducted for the 2018 update of the WHO LTBI treatment guidelines

Assessment

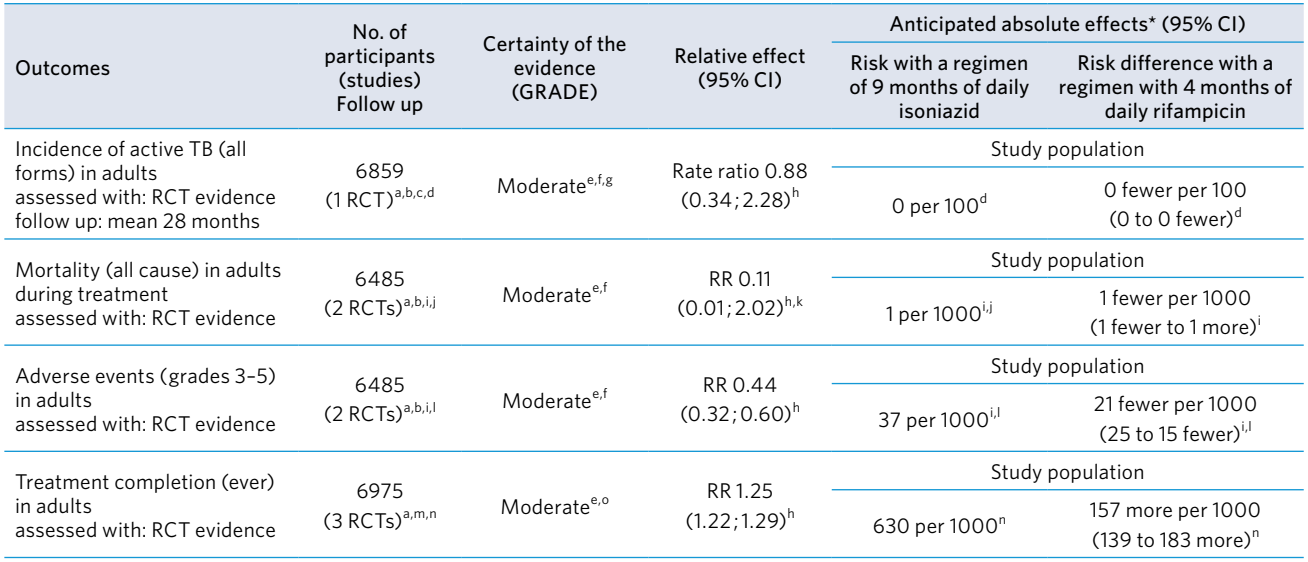
Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	About one fourth of the world's population is estimated to have LTBI, but the levels may be much higher in certain populations and high TB burden settings. Treatment of LTBI can reduce an individual's risk of developing active TB.	The GDG agrees that with the tools available today for scaling up LTBI treatment worldwide will be critical to reducing global TB incidence to the levels envisaged by the WHO End TB Strategy, and to remove the global public health problem represented by TB today. Safer, more effective LTBI regimens that are easier to use can contribute to achieving this end.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		The GDG members reached agreement that the desirable effects of use of 4R as a LTBI option would be small, but not inferior to 9H. The efficacy of the 4R regimen in the trials suggests that it could be considered as an option for preventive treatment in both low and high resource settings, regardless of age. This implies that 4R could be an alternative not only to 9H, which is how it was investigated in the trials, but to other TPT regimens based on a broader judgement of the circumstances and other options available to people requiring LTBI treatment.

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with a regimen of 9 months of daily isoniazid	Risk difference with a regimen with 4 months of daily rifampicin
Incidence of active TB (all forms) in adults assessed with: RCT evidence follow up: mean 28 months	6859 (1 RCT)[a,b,c,d]	Moderate[e,f,g]	Rate ratio 0.88 (0.34; 2.28)[h]	Study population	
				0 per 100[d]	0 fewer per 100 (0 to 0 fewer)[d]
Mortality (all cause) in adults during treatment assessed with: RCT evidence	6485 (2 RCTs)[a,b,i,j]	Moderate[e,f]	RR 0.11 (0.01; 2.02)[h,k]	Study population	
				1 per 1000[i,j]	1 fewer per 1000 (1 fewer to 1 more)[i]
Adverse events (grades 3–5) in adults assessed with: RCT evidence	6485 (2 RCTs)[a,b,i,l]	Moderate[e,f]	RR 0.44 (0.32; 0.60)[h]	Study population	
				37 per 1000[i,l]	21 fewer per 1000 (25 to 15 fewer)[i,l]
Treatment completion (ever) in adults assessed with: RCT evidence	6975 (3 RCTs)[a,m,n]	Moderate[e,o]	RR 1.25 (1.22; 1.29)[h]	Study population	
				630 per 1000[n]	157 more per 1000 (139 to 183 more)[n]

Incidence of active TB (in all forms) in paediatrics assessed with: RCT evidence follow up: mean 16 months	829 (1 RCT)[p,q]	Moderate[e,r,s]	Rate ratio 0.19 (0.01 to 4.02)[h,t]	Study population	
				5 per 1000	4 fewer per 1000 (5 fewer to 15 more)
Mortality (all cause) in paediatrics during treatment assessed with: RCT evidence	829 (1 RCT)[p,q]	MODERATE[e,s]	RR 2.89 (0.12 to 70.82)[h,k]	Study population	
				0 per 1000	0 fewer per 1000 (0 to 0 fewer)
Adverse events (grades 3–5) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	MODERATE[e,s]	RR 0.96 (0.06 to 15.37)[h]	Study population	
				2 per 1000	0 fewer per 1000 (2 fewer to 35 more)
Adverse events (related grades 3–5) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	MODERATE[e,s]	RR 0.96 (0.02 to 48.50)[h,k]	Study population	
				0 per 1000	0 fewer per 1000 (0 to 0 fewer)
Treatment completion (ever) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	Moderate[e,o]	RR 1.12 (1.05 to 1.20)[h]	Study population	
				771 per 1000	93 more per 1000 (39 to 154 more)
Incidence of active TB (in all forms) in HIV-positive adults assessed with: RCT evidence follow up: mean 28 months	270 (1 RCT)[a,b,c,d,u]	Low[e,f,v]	Rate ratio 0.48 (0.04 to 5.29)[h]	Study population	
				14 per 1000[d,u]	8 fewer per 1000 (14 fewer to 62 more)[d,u]
Adverse events (grades 3–5) in HIV-positive adults assessed with: RCT evidence	268 (2 RCTs)[a,b,u,w]	Low[e,f,v]	RR 0.27 (0.06 to 1.23)[h]	Study population	
				58 per 1000[u,w]	42 fewer per 1000 (54 fewer to 13 more)[u,w]

[a] Phase 2 *(64)* and Phase 3 *(62)* open-label trials conducted in nine countries, assigning adults with latent TB infection to receive treatment with a 4-month regimen of daily rifampicin or a 9-month regimen of daily isoniazid. The primary outcome in the phase 2 trial was incidence of grades 3–5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active TB within 28 months of randomization. The primary outcome of the phase 3 trial was microbiologically confirmed active TB within 28 months of randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active TB, grades 3–5 adverse events and treatment completion. Outcomes of active TB and adverse events were adjudicated by three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits.

[b] No significant difference in guidelines or risk profiling of latent TB reactivation was found between the phase 2 and phase 3 trials in adults in terms of judging "increased risk for reactivation". Randomization in both trials was stratified by site and centrally computer-randomized. Patients were randomized 1:1 in blocks of varying length (2–8) to isoniazid or rifampicin.

[c] The GDG decided that for efficacy outcomes the pooled outcomes of phase 2 and phase 3 studies be considered one trial as the same protocol was used for both phases conducted by the same investigating team, even if more sites were used in the phase 3 study. Although the quality was not downgraded for this, the GDG noted that Inconsistency could not be judged, given that there was only a single trial. Ideally, replication by other trials would be desirable. For adverse events the studies can be considered as two separate trials *(62)*.

[d] All active TB events occurred within the phase 3 trial *(62)*.

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

The trial compared 4R with 9H. However, in many settings where LTBI treatment is used at scale, the normal standard of care would be 6H (i.e. 3 months shorter than 9H).

The comparison of 4R with 9H is thus more likely to favour the 4R regimen than if the comparator had been 6H, which being shorter than 9H would be expected to generate less adverse reactions and be easier to complete. Conversely, 9H may be more effective than 6H in preventing TB; if so, 4R would have performed better had the trial had a 6H control. Some GDG members considered that the difference between 4 months and 6 months of treatment remains important and could improve adherence, even if the completion rates reported in the trial are unlikely to be feasible under programmatic conditions at large scale.

The GDG decided that the phase 2 and phase 3 adult studies be considered a single trial for the efficacy estimates.

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

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

[h] Unadjusted estimate.

[i] Denominators are representative of the combined safety population of phase 2 *(64)* and phase 3 *(62)* as indicated in supplemental tables S2 and S3 of the phase 3 publication. In the phase 2 trial, 396 patients receiving isoniazid and 393 patients receiving rifampicin formed the safety population; in the phase 3 trial, 2809 patients receiving isoniazid and 2887 patients receiving rifampicin formed the safety population.

[j] All deaths occurred in the phase 3 trial *(62)*.

[k] A zero cell correction of 0.5 was used to calculate the risk ratio.

[l] In the phase 2 trial *(64)*, 10 patients receiving rifampicin experienced grade 3–5 adverse events that led to permanent discontinuation of the medication, of which 7 were deemed possibly or probably related to the study drug; 19 patients receiving isoniazid experienced grade 3–5 adverse events, which led to permanent discontinuation of the medication, of which 16 were deemed possibly or probably related to the study drug. In the phase 3 trial *(62)*, 43 patients receiving rifampicin experienced grades 3–5 adverse events that led to permanent discontinuation of the medication, of which 24 were deemed possibly or probably related to study drug; 100 patients receiving isoniazid experienced grade 3–5 adverse events that led to permanent discontinuation of the medication, of which 59 were deemed possibly or probably related to study drug.

[m] Also included is the phase 1 trial *(65)*, a single centre, open-label randomized trial of the superiority of 4 months of daily rifampicin to 9 months of daily isoniazid for treatment completion.

[n] Numerator and denominator values are derived from the phase 1 trial *(65)*, phase 2 trial *(64)* and phase 3 trial *(62)*. Treatment completion was defined as taking at least 80% of prescribed doses (i.e. at least 96 pills of rifampicin or 216 pills of isoniazid). In the phase 1 trial, 44 of 58 individuals randomized to isoniazid and 53 of 58 randomized to rifampicin completed treatment. In the phase 2 trial, 254 of 427 individuals randomized to isoniazid and 328 of 420 randomized to rifampicin completed treatment. In the phase 3 trial, 1890 of 2989 individuals randomized to isoniazid and 2382 of 3023 individuals randomized to rifampicin completed treatment.

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

[p] Open-label, non-inferiority trial conducted in seven countries, assigning children with latent TB infection to receive treatment with a 4-month regimen of rifampicin or a 9-month regimen of isoniazid for the incidence of grades 3–5 adverse events during treatment. Secondary outcomes were the incidence of microbiologically confirmed active TB within 16 months of randomization and completion of the treatment regimen. Outcomes of active TB and adverse events were adjudicated by two- or three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits *(62)*.

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

[r] Among those randomized to isoniazid and forming the modified intention-to-treat population, six individuals were lost to follow-up. Among those randomized to rifampicin and forming the modified intention-to-treat population, five individuals were lost to follow-up. Of all children forming the modified intention-to-treat population, 1.3% were lost to follow-up.

[s] Open label design but endpoints of active TB and adverse events adjudicated by two-member and three-member, respectively, independent, blinded review panels. There were nine per protocol exclusions among those randomized to isoniazid and six per protocol exclusions among those randomized to rifampicin, due to a negative TST 2 months after exposure. The GDG decided to downgrade the study by one level because of the open label design and because some sites were not high burden.

[t] A zero cell correction of 0.5 was used to calculate the rate ratio.

[u] Denominators include HIV-positive patients known at the time of randomization as reported in Supplemental Table S1 of the phase 3 adult trial *(63)*, and patients diagnosed post-randomization as a result of baseline assessment. These included 130 patients and 8 patients receiving isoniazid with an HIV-diagnosis at time of randomization and post-randomization, respectively, and 125 patients and 7 patients receiving rifampicin with an HIV-diagnosis at the time of randomization and post-randomization, respectively. This resulted in modified intention-to-treat population sizes of 132 for rifampicin and 138 for isoniazid. Among HIV-positive patients randomized to rifampicin, 2 did not receive a dose of therapy. Thus, the safety population sizes were 130 for rifampicin and 138 for isoniazid.

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

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

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See tables above	Rifampicin is generally well tolerated, and the 4R regimen had a good safety profile in the trials. The 4R regimen has been recommended by WHO for use in low TB incidence settings. The GDG agreed that the anticipated undesirable effects would be moderate for the 4R vs. 9H regimen. The likelihood that active TB could be reliably excluded in a high TB burden, low income setting is lower than in a better resourced situation. If the "rule out" algorithm for active TB is inadequate (e.g. limited to symptom screen and without CXR), active TB may be inadvertently treated with 4R. There is therefore a greater risk that people with active TB receive rifampicin monotherapy. Another important concern is the effect that rifampicin could have on other medications and substances administered concurrently.

		Interactions with ART in PLHIV (e.g. efavirenz, dolutegravir), with alcohol, with oral or injectable contraceptive medicines in women of childbearing age and with methadone in people on opioid replacement are the most likely situations in which significant drug-drug interactions with rifampicin are to be expected. If loose tablets of rifampicin are used more broadly to treat bacterial infections, resistance may be propagated. Although a risk is present, there is little evidence that broad scaling up of LTBI treatments such as 4R would generate TB drug resistance.
Certainty of evidence		
What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty of the estimates of effect (quality of evidence) was MODERATE for four outcomes considered CRITICAL or IMPORTANT by the GDG in both adults and children: active TB, treatment completion, adverse events of grade 3 or more, and mortality; however, quality was LOW for all outcomes in HIV-positive adults because of additional downgrading due to imprecision (small numbers of observations in this sub-group and not stratified at randomization). Insufficient cases were available to assess the risk of emergent drug resistance. No outcome was considered of HIGH certainty because of: possible risk of bias from the open label design (even if this was partly mitigated by a blinded expert panel assessment of active TB and adverse events); other risk of bias from a single study by one trial group; possible indirectness given that the comparator is 9H rather than the 6H regimen, which is more widely used in LTBI care.	The GDG concluded that the overall certainty in the evidence was MODERATE. Inconsistency could not be judged, as there was a single trial; even if the study was conducted in several countries, the GDG considered that confidence in the findings would be increased if the findings can be replicated on other studies, especially in PLHIV.

Values		
Is there important uncertainty about or variation in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variation ○ Possibly important uncertainty or variation ● Probably no important uncertainty or variation ○ No important uncertainty or variation	The trials did not include an untreated group as a comparator.	The GDG considered that a shorter regimen would be welcomed by most people. The GDG considered that there is probably no important uncertainty or variation in how most people value the outcomes, but that this may differ between subgroups, such as PLHIV on ARVs and women on contraceptive medicines. Given that the 4R regimen is already recommended and that rifampicin is a component of other LTBI treatment, it considered that there is less uncertainty about how best to use this regimen (e.g. dosage, drug–drug interactions) than for newer ones.
Balance of effects		
Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		The GDG considered that, overall the intervention would be favoured in many settings, regardless of the burden and required resources. A shorter LTBI treatment is likely to decrease adverse events and could reduce the risk of emergence of drug resistance. Concern was expressed about the uncertainty of effect in people in whom rifampicin is contraindicated or in settings where rifampicin-resistance is rife. In such situations, other LTBI treatment options should be considered.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	The WHO recommended dosages for the 4R regimen are 10 mg/kg per day for adults and 15 mg/kg per day (range, 10–20 mg) for children. At current Global Drug Facility (GDF) cost, a full course of 4R for an adult weighting > 50 kg would cost US$24. In contrast in an adult >50kg, 9H costs about US$5, 3HR about US$13 (US$10 in a child (12–15kg)), 3HP costs about US$46, and 1HP about US$70 [as in **August 2019**]. The 4R regimen is likely to require several visits during treatment, which may add costs over those with shorter rifamycin regimens such as 1HP and 3HP.	The GDG considered that resource use will depend primarily on programmatic circumstances, such as the degree of integration into primary health care and adjustments made to accommodate the new regimen. Judging by the drug costs alone as per GDF prices, for which many low resource countries would be eligible, the 4R regimen in adults would cost about five times as much as the 9H regimen, slightly more than the 3HR regimen (which can be delivered as an inexpensive fixed dose combination), and two to three times cheaper than 3 months of weekly rifapentine and isoniazid (3HP) or 1HP regimen respectively. In addition to the GDF drug costs, the GDG examined data collected and analysed by the coordinators of the 4R vs 9H studies (see tables at left) of health system costs for both regimens by comparing clinical activities, including visits, tests, imaging studies and treatment for people randomized to 4R or 9H. In these trials, 6012 adults and 829 children were included in the mITT populations. Parameters used in the calculations (e.g. higher completion of 4R vs. 9H) reflected observations from the trials. For each study participant, the number of times each activity was performed was multiplied by the unit cost (in Canadian dollars (CAD)) and individual costs were then summed for a total cost per participant. The source of drug costs was the Global Drug Facility catalogue. Other costs reflect those at the Montreal Chest Institute,

Costs by LTBI regimen at all sites for paediatric patients. *(The source of costs for all tests and activities is Régie de l'assurance maladie du Québec, Canada)*

	4R		9H		
	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Ratio of mean costs per MITT patient (4R/9H) 95% CI[a]
N patients (MITT)	422		407		
Baseline evaluation					
Visits	518 63.80	122.90 (0)	50 020.30	122.90 (0)	1.00
Blood tests	9 223.78	21.85 (0.64)	8 933.76	21.95 (0.14)	1.00
Imaging studies	11 072.20	26.23 (2.82)	10 622.70	26.10 (0)	1.00
Procedures	0	-	151.48	0.37 (7.51)	
TB microbiological tests	493.46	1.17 (12.53)	159.26	0.39 (5.25)	3.00
Follow-up during treatment					
Drugs (INH or RIF only – GDF prices)	9 196.22	21.79 (9.21)	3335.31	8.19 (3.83)	2.66
Visits	101 255.21	239.94 (68.93)	191 811.17	471.28 (177.12)	0.51
Blood tests	617.33	1.46 (6.843)	343.84	0.84 (2.09)	1.74
Imaging studies	156.60	0.37 (3.09)	234.90	0.57 (4.63)	0.65
Other microbiological tests	21.950	0.05 (1.06)	26.74	0.07 (1.11)	0.71
Costs of adverse events care					
Visits	0	-	68.25	0.16 (3.38)	
Blood tests	0	-	7.10	0.02 (0.35)	
Total costs					
All patients/events	183 900.55	435.78 (76.51)	265 714.81	652.86 (179.94)	0.66 (0.64, 0.69)
Except adverse events	183 900.55	435.78 (76.51)	265 639.46	652.67 (180.04)	0.66 (0.64, 0.69)
Adverse events only	0	-	75.35	0.18 (3.73)	-

[a] Confidence intervals calculated using the Fieller theorem *(66)*.

Estimated costs by LTBI regimen for all adults in Phase 3, at all sites. *(The source of information for the costs for all tests and clinical activities is Régie de l'assurance maladie du Québec, Canada – hence relative costs are more informative than absolute costs, or differences in costs)*

	4R		9H		Ratio of mean costs per MITT patient (4R/9H) 95% CI[a]
	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	
No. of patients (mITT)	3 023	–	2 989	–	
Baseline evaluation					
Visits	616 692.00	204.0	609 756.00	204.0	1.00
Blood tests	96 867.75	32.04 (19.4)	94 966.93	31.8 (19.2)	1.01
Imaging studies	81 271.00	26.8 (9.7)	80 472.10	26.9 (6.8)	1.00
Microbiological tests	42 142.20	13.9 (55.2)	40 488.72	13.5 (54.5)	1.03
Follow-up during treatment					
Drugs (INH or RIF only)	79 434.94	26.27 (9.98)	17 665.50	5.91 (3.05)	4.4
Visits	757 090.20	250.44 (106.42)	1 234 874.00	413.13 (231.20)	0.61
Blood tests	83 476.21	27.61 (23.37)	99 281.90	33.21 (37.09)	0.83
Imaging studies	3 884.35	1.28 (7.24)	4 332.6	1.44 (10.01)	0.89
TB Microbiological tests	722.54	0.23 (6.80)	1 625.41	0.54 (17.0)	0.43
Other microbiological tests	31.53	0.01 (0.40)	71.81	0.02 (0.82)	0.50
Procedures	472.40	0.15 (7.03)	201.74	0.06 (1.75)	2.50
Costs for AE care					
Visits	10 731.52	3.549 (29.81)	20 978.5	7.01 (39.19)	0.51
Blood tests	2 700.37	0.89 (9.38)	9 044.14	3.02 (19.63)	0.29
Imaging studies	312.30	0.10 (2.68)	2 776.80	0.92 (9.86)	0.11
Specialist consultations	688.64	0.22 (6.12)	1 396.72	0.47 (11.22)	0.47
Microbiological tests	21.95	0.007 (0.399)	113.04	0.037 (1.32)	0.19
TB microbiological tests	0	–	15.68	0.005 (0.28)	
Procedures	0	–	2 232.75	0.746 (30.95)	
Hospitalization days	8264.40	2.73 (107.73)	35 812.40	11.98 (365.39)	0.23
Total costs					
All patients/events	1 784 804.30	590.41 (188.71)	2 256 106.74	754.82 (475.77)	0.78 (0.76, 0.80)
Except adverse events	1 762 085.12	582.89 (148.28)	2 183 736.89	730.59 (264.28)	0.80 (0.79, 0.81)
Adverse events only	22 719.18	7.51 (128.97)	72 370.03	24.21 (407.63)	0.31 (0.11, 0.86)

[a] Confidence intervals calculated using the Fieller theorem *(66)*.

Québec, Canada. The salaries of nurses and other health-care workers were taken from salary scales and physician payments from provincial reimbursement fee schedules in Canada. Given these different sources of data, many of which are from a high resource setting, the ratios of mean costs of 4R vs 9H rather than the absolute values may be more useful for assessing the global implications of the 4R regimen on resource use.

The overall ratio of mean costs of 4R vs 9H was 0.66 in children and 0.78 in adults included in the mITT populations of the phase 3 trials at all sites. The ratio of adverse event management alone in adults was 0.31. Clinic visits and blood tests were major determinants of overall cost in both arms.

The GDG observed that, while this analysis was informative, it related only to costs in a trial setting and that programmatic realities could modify the costs substantively. For example, combination of visits with other encounters with health services could result in important cost savings. Visits could also be cheaper in low resource settings than in high income countries. The GDG therefore voted for a variable range of resource requirements in different settings, from moderate costs to moderate savings. Nonetheless, the GDG noted that cost should not be considered an absolute barrier if there were other important benefits that could not be appropriately expressed in monetary terms. Some costs (e.g. in the cost of medicines) may change over time.

Certainty of evidence of required resources		
What is the certainty of the evidence of resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	See above	The GDG considered that despite the studies and data on certain resource requirements of the 4R regimen there is low certainty about how widely applicable the information is to the places where the regimen will be used.
Cost effectiveness		
Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies		The GDG agreed that a full cost effectiveness analysis with a longer horizon for effects and looking at different populations and settings would be important.
Equity		
What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No included studies	The GDG considered that this regimen is likely to be used without additional resources secured ahead of its introduction and there is therefore a risk its higher price could reduce access to treatment and to other health care services for all people that depend on the same resources. It is therefore possible that equity may be reduced, with certain subgroups benefiting from 4R at the expense of others in whom the regimen is relatively or absolutely contraindicated or in whom ruling out of active TB is more difficult and are therefore more likely to be offered another treatment option.

		Any gains in equity could also change over time if policy in the use of 4R changes. On the other hand, the shorter duration of treatment could mean that more people complete their treatment and therefore protection is more complete and equity is increased for people at risk. The GDG agreed that the introduction of 4R needs to be accompanied by mobilization of appropriate resources from start to avoid shortages in different competing health care needs.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		The GDG considered that programmes may be reluctant to use 4R widely out of concerns of increasing drug resistance in settings where screening for active TB has a poor sensitivity. They may also not want to reintroduce single dose preparations of rifampicin to prevent misuse as a broad-spectrum antibiotic. The higher price of 4R medicines could lower its acceptability compared to alternative LTBI treatments. Conversely, the GDG considered that a shorter regimen may be more acceptable to both the health services and to people at risk without contraindications. The 4R regimen is already recommended by WHO for low incidence settings. Rifampicin is also a component of 3HR, another recommended LTBI regimen in children and adults. The safety profile of rifampicin is very well known and accepted as a medicine for the treatment of active TB.

Feasibility		
Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		The GDG considered that the most important, immediate barrier to the feasibility of 4R in many high TB burden settings would be the procurement of affordable, quality-assured, single-dose formulations of rifampicin. In some countries that do not use fixed dose combination to treat TB then this challenge may be less important or not applicable. Additional requirements (e.g. direct in-person observation of doses) are expected to influence feasibility as well as acceptability.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variation	Possibly important uncertainty or variation	**Probably no important uncertainty or variation**	No important uncertainty or variation			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	**Probably no**	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

Conclusions

Recommendation

A regimen with four months of daily rifampicin may be used as preventive treatment in people at risk of active TB
(conditional recommendation; moderate confidence in the estimates of effect)

Justification

When formulating this recommendation, the GDG considered primarily data from the randomized controlled trials (RCT) of the 4R regimen that included sites in high TB burden settings *(62–65)*. The 4R regimen had already been recommended by WHO for low TB incidence settings by the time the results of the phase 3 trials in children and adults were released in 2018. Phase 2 *(64)* and phase 3 *(62,63)* open-label RCTs have been conducted in nine countries (Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and Republic of Korea), assigning children (0–17y) and adults (18y and more) with LTBI to receive treatment with 4R or 9H. In adults, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was <0.01 cases per 100 person-years (95% confidence interval [CI], −0.14; 0.16); the difference in treatment completion was 15.1% (95% CI, 12.7; 17.4); the difference for Grade 3–5 adverse events was −1.1% (95% CI, −1.9; -0.4). In children, the difference in rate of active TB between 4R and 9H was -0.37 cases per 100 person-years (95% CI, −0.88; 0.14); the difference in treatment completion was 13.4% (95% CI, 7.5; 19.3); the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was −0.0 (95% CI, −0.1; 0.1).

Out of the 17 GDG members, 13 expressed their views on this regimen during the GDG meeting and all were in favour of a conditional recommendation. The GDG considered that there was moderate certainty that 4R is not inferior to 9H, and when also considering the good safety profile of the 4R regimen and its reduced length, it recommended that this regimen also be used in high TB-burden settings. The GDG considered that most people would value the shorter regimen, but raised concerns regarding variation in acceptability, uncertainty in resources requirements, and potential for reducing equity, leading to a conditional recommendation.

Subgroup considerations

Drug-drug interactions: rifampicin induces certain cytochrome P-450 enzymes and may therefore interfere with many medicines that depend on this metabolic pathway, accelerating their elimination. Apart from ARVs (see below), these include anticonvulsants, antiarrhythmics, oral anticoagulants, antifungals, corticosteroids, cyclosporine, fluoroquinolones and other antimicrobials, oral hypoglycaemic agents, and tricyclic antidepressants. These medicines may therefore need to be avoided while 4R is given or their dosages adjusted. At times the interaction may lead to increased or decreased concentrations of rifampicin itself.

PLHIV: the phase 3 trial evidence reviewed for this recommendation included adults with HIV (4% in each arm of the mITT population) but no children (HIV infection was not an exclusion criterion). The GDG considered however that the recommendation can apply to adults and children with HIV, subject to cautions that apply generally to people taking ARVs with rifampicin. No dose adjustment is required when rifampicin is co-administered with efavirenz. The dose of dolutegravir however needs to be increased to 50 mg twice daily when given together with rifampicin *(67),* a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz. Rifampicin can decrease the concentrations of other antiviral drugs: atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir. It should not be used with saquinavir/ritonavir. A key contraindicated drug combination is rifampicin with PIs. A decision on use of 4R in PLHIV on ARVs requires expertise in clinical management of HIV.

Other populations: the trials reviewed for this recommendation showed 4R to be safe for use in children (0-17y) as a TB preventive regimen. Rifampicin is generally considered safe in pregnancy. In candidates for transplantation or anti-TNF treatment it may be particularly important to complete LTBI treatment fast and therefore 4R could have an advantage over longer treatments. In homeless people and in prisoners being released from detention, given the limited opportunity to have repeat encounters, 4R could also be more suitable than longer regimens. In addition to PLHIV on ARVs, other populations who may be more commonly at risk of drug-drug interactions include women of childbearing age on oral or injectable contraceptive medicines (who may need to consider nonhormonal methods of birth control during 4R) and opiate users on methadone replacement. Concurrent use of alcohol needs to be avoided.

Implementation considerations

The GDG considered that the 4R regimen could be offered to people eligible for LTBI treatment regardless of the TB burden setting. It should be considered not only as an alternative to 9H, which is how it was investigated in the trials reviewed, but in broader circumstances for people requiring LTBI treatment. The choice of regimen is usually based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity or interaction, co-morbidity, availability and preferences. Translation of the findings of trials to programmatic realities will be critical. More advice on recommended treatment is provided in the respective WHO operational guidance.

One of the major concerns expressed by health care providers to use 4R is the risk of administering it inadvertently to people who have active TB. This is to be avoided as it may lead to disease chronicity and favour the emergence of drug resistance. As for any TPT a robust algorithm to rule-out active disease is necessary.

Given the widespread use of rifampicin-containing fixed dose combinations to treat drug-susceptible TB, single dose rifampicin has become less available to disease programmes. If the 4R regimen will be used more often the demand for loose tablets of rifampicin will increase and programmes would need to procure it. Quality-assured supplies of rifampicin should be used. The provision of 4R to other centres (e.g. primary care facilities, HIV programmes) should be accompanied by stepwise guidance on how to use it and how to protect rifampicin (e.g. not to divert it for use as a broad-spectrum antibiotic).

The dosage recommended for 4R is 10 mg/kg/day in adults and 15 mg/kg/day (range, 10–20 mg) in children.

No data-supported recommendations exist on how to handle interruptions of 4R, i.e. if missed doses are added at the end and after how many missed doses to start afresh.

In areas with high background resistance to rifampicin, such as countries in eastern Europe, it is particularly important to test the presumed infecting strain from the source case so that treatments given are more likely to work. If there is monoresistance or other contraindications to rifampicin, then an isoniazid regimen of 6 or more months would be the most likely alternative to give. Unfortunately, in many settings, rifampicin resistance is often accompanied by isoniazid resistance – multidrug-resistant TB (MDR-TB) – requiring a different approach to preventive medication (see section 1.4 of the guidelines document).

Monitoring and evaluation

The framework to monitor and evaluate the programmatic management of LTBI applies for the use of regimens such as 4R. Rifampicin has been generally well-tolerated and the 4R LTBI regimen has shown a good safety profile in trials when compared to more widely used regimens. The 4R regimen has been previously recommended by WHO for low incidence settings.

As individuals who receive LTBI treatment do not have active disease, their risk for adverse events during treatment must be minimized. 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.

While most reactions are minor and not serious, attention should be paid in particular to prevent drug-induced hepatotoxicity. Monitoring should focus on liver function. There is no justification to test liver function at baseline in all people to be started on LTBI treatment, but it should be 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, clinical judgement is required to assess if benefit of TPT outweighs the risks; 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). Trial criteria for when to stop rifampicin – e.g. an increase in transaminases to 5 times the upper limit of normal or to 3 times plus symptoms – will need to be adapted to something more practical under field conditions.

Monitoring for adherence to the full course of LTBI treatment and its completion are important determinants of clinical benefit to individuals and to the success of programmes. The shorter duration of 4R makes it more likely to be completed. Interventions to enhance adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. Concerns about adherence should not be a barrier to use of preventive treatment. The 2017 WHO guidelines for the treatment of drug-susceptible TB propose several interventions to support adherence in patients with active TB, which could be applied to treatment of LTBI. An electronic application for mobile phones has been created by WHO to guide national programmes on critical data to collect along the LTBI care pathway, as an accessory to monitoring and evaluation.

It would be helpful to collect information about the occurrence of active TB in people who have received 4R or other LTBI treatment. This can be done by asking patients registered for treatment about any history of starting or completing LTBI treatment or the cross linkage of registers (e.g. LTBI registers and TB treatment registers or mortality register). In people who develop TB after 4R treatment, or people found to have active TB well into their LTBI treatment, it would be helpful to monitor also for emergence of resistance.

Research priorities

- More evidence on the performance of 4R in populations who have not been studied or with limited data: adults and children with HIV on ARV; pregnancy
- Comparison of safety and effectiveness with future trials and other studies performed under different conditions and populations
- Durability of effect in different settings and generation of resistance when different LTBI regimens are used, including those containing R
- Implementation research on context-specific barriers and facilitators for 4R at programme level (acceptability, feasibility, equity, resource use)
- Pharmacokinetics of rifampicin with other medicines in adults and children
- Cost effectiveness analysis using parameters from both high and low resource settings

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

Population:	In people of all ages at risk of active TB
Intervention:	A regimen with one month of daily rifapentine plus isoniazid ("1HP")
Comparison:	Another regimen (9-months of isoniazid alone [9H] for the study identified and reviewed)
Main outcomes:	Outcomes scored as critical or important by the GDG were: active TB incidence, mortality, adverse events, treatment completion, emergence of drug resistance
Setting:	For this PICO question the GDG considered data from the only known published study of this regimen – **BRIEF-TB/A5279** – a randomized, open-label, phase 3 non-inferiority controlled trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI *(68)*. Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. The primary end-point of this trial was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. LTBI was not confirmed in about 80% of participants. Overall TB incidence observed in the trial was lower than expected. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30); the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority was thus shown; likewise non-inferiority was shown separately for the sub-groups with confirmed LTBI infection, males and females, and for those on or without ARV at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. The outcomes extracted from the trial to address the ones in the PICO were the following (see also the GRADE evidence summary table for PICO 7 in Annex 3): Incidence of active TB; Incidence of active TB among ART-naive participants at entry; Incidence of active TB among TST or IGRA positive participants at entry; Incidence of bacteriologically confirmed TB; Time to TB diagnosis or death related to TB (with other deaths treated as competing risk); Incidence of active TB or death due to unknown cause; Incidence of active TB or death due to unknown cause; Incidence of active TB or death from any cause; Time to death from any cause; Time to death from tuberculosis; Adverse events (grade 3 or higher of nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy); Serious adverse events; Treatment completion; Treatment completion among ART-naive participants at entry; Emergence of drug resistance to isoniazid among those with confirmed TB and with DST; Emergence of drug resistance to rifampicin among those with confirmed TB and with DST; Emergence of drug resistance to ethambutol among those with confirmed TB and with DST; Emergence of drug resistance to pyrazinamide among those with confirmed TB and with DST

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	About one quarter of the world's population is estimated to have LTBI, but the levels may be much higher in certain populations and high TB burden settings. Treatment of LTBI can reduce an individual's risk of developing active TB.	The GDG agreed that, with the tools available today, scaling up of LTBI treatment worldwide will be critical to reducing global TB incidence to the levels envisaged in the WHO End TB Strategy and to removing the global public health problem represented by TB. Safer, more effective LTBI regimens that are easier to implement will play an important role.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See table below	The GDG members reached agreement that the desirable effects of using 1HP as a LTBI option would be moderate given the notable reduction in treatment time with non-inferior performance. The efficacy of the 1HP regimen shown in the trial suggests that it could be considered as an alternative for TPT in both low and high resource settings, at least in populations with the same profile as those included in the study, i.e. adolescents and adults with HIV who were not pregnant or breast-feeding. The trial compared 1HP with 9H. However, in many settings where LTBI treatment is used at scale, the normal standard of care would be 6H (i.e. 3 months shorter than 9H).

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with nine months daily isoniazid	Risk difference with one month daily rifapentine plus isoniazid
Incidence of active TB assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	2986 (1 RCT)	Low[a,b,c]	Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)	Study population 17 per 1000	16 fewer per 1000 (22 to 11 fewer)
Incidence of active TB among ART-naive participants at entry assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	1486 (1 RCT)	Low[a,b,c]	Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)	Study population 20 per 1000	19 fewer per 1000 (28 to 10 fewer)

Incidence of active TB among TST or IGRA positive participants at entry assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	686 (1 RCT)	Low[a,b,c]	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	Study population 29 per 1000	31 fewer per 1000 (52 to 9 fewer)
Incidence of bacteriologically confirmed TB assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	2986 (1 RCT)	Low[b,c,d]	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	Study population -- per --	-- per -- (-- to --)
Time to TB diagnosis or death related to TB, with other deaths treated as competing risk assessed with: RCT evidence (mITT population) follow up: mean 3 years	2986 (1 RCT)	Low[c,e]	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	Low 17 per 1000f	2 more per 1000 (6 fewer to 15 more)
Incidence of active TB or death due to unknown cause assessed with: RCT evidence (mITT population) follow up: mean 3 yearsg	2986 (1 RCT)	Low[c,h]	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	Study population 22 per 1000	23 fewer per 1000 (30 to 15 fewer)
Incidence of active TB or death due to unknown cause assessed with: RCT evidence (per-protocol population) follow up: mean 3 years	2837 (1 RCT)	Low[c,h]	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	Study population 21 per 1000	21 fewer per 1000 (27 to 14 fewer)
Incidence of active TB or death from any cause assessed with: RCT evidence (mITT population) follow up: mean 3 years	2986 (1 RCT)	Low[b,c]	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	Study population -- per --	-- per -- (-- to --)
Time to death from any cause assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	Low[b,c,h]	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	Low 19 per 1000[f,i]	5 fewer per 1000 (11 fewer to 6 more)
Time to death from tuberculosis assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	Very low[b,c,j]	HR 1.00 (0.20 to 4.93)	Study population 2 per 1000	0 fewer per 1000 (2 fewer to 8 more)

This comparison is thus more likely to favour the 1HP regimen than if the comparator had been 6H, which being shorter than 9H would be expected to generate less adverse reactions and be easier to complete, even though the difference in length between 1 month and 6 months remains substantial. Conversely, 9H may be more effective than 6H in preventing TB and if so 1HP would have performed better had the trial used a 6H control. The 1 month duration is also a substantial reduction from the 3 month minimum length of other shorter LTBI regimens currently approved.

Some GDG members remarked that the adherence observed in the trial is unlikely to be reproduced under programmatic conditions at large scale. The study design could only show non-inferiority so the difference from the comparator under field conditions may not be of public health significance.

Adverse events (grade 3 or higher of nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy) assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	Low[b,c]	RR 0.86 (0.58 to 1.27)	Study population	
				35 per 1000	5 fewer per 1000 (15 fewer to 9 more)
Serious adverse events assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	Low[b,c]	RR 0.79 (0.59 to 1.04)	Study population	
				72 per 1000	15 fewer per 1000 (30 fewer to 3 more)
Treatment completion assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	Low[b,c,k]	RR 1.04 (0.99 to 1.10)	Study population	
				895 per 1000	36 more per 1000 (9 fewer to 90 more)
Treatment completion among ART-naive participants at entry assessed with: RCT evidence follow up: mean 3 years	1483 (1 RCT)	Low[b,c,k]	RR 1.05 (0.97 to 1.14)	Study population	
				883 per 1000	44 more per 1000 (26 fewer to 124 more)
Emergence of drug resistance to isoniazid among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	26 (1 RCT)	VERY Low[b,c,l,m]	RR 1.63 (0.17 to 15.99)	Study population	
				83 per 1000	52 more per 1000 (69 fewer to 1,249 more)
Emergence of drug resistance to rifampicin among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	27 (1 RCT)	Very low[b,c,l,m]	RR 0.81 (0.06 to 11.77)	Study population	
				83 per 1000	16 fewer per 1000 (78 fewer to 898 more)
Emergence of drug resistance to ethambutol among those with confirmed TB and with DST	14 (1 RCT)	Very low[b,c,l,m]	not estimable	Study population	
				143 per 1000	143 fewer per 1000 (143 to 143 fewer)
Emergence of drug resistance to pyrazinamide among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	12 (1 RCT)	Very low[b,c,l,m]	not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 to 0 fewer)

[a] Unknown cause of death censored in this analysis, which may cause bias in incidence rate difference if some of these deaths were related to TB (dependent censoring)
[b] The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 1HP with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TPT. The GDG noted that Inconsistency could not be judged given that there was only a single trial; results from more trials would be desirable.
[c] Trial conducted only in PLHIV and not all people at risk of active TB.
[d] Probable TB diagnoses and deaths with non-bacteriologically confirmed TB censored at the time of event
[e] When cause of death was determined to be unknown or not related to TB by blinded external reviewers, these were treated as a competing risk rather than endpoint. Some of these may have actually been due to TB, which may bias estimate.
[f] The proportion of events among controls
[g] Per-protocol population consisted of all participants who completed treatment, or who had died or received a TB diagnosis while they were receiving treatment.
[h] Deaths were reviewed by blinded external reviewers. Unknown causes of death were included as an endpoint, but misclassification of cause of death may bias estimate
[i] There were 21 deaths in the one-month arm, 3 related to TB. There were 28 deaths in the nine-month arm, 3 related to TB.
[j] Small number of events
[k] Assessed via participant self-report at clinic visits
[l] Resistance may be non-emergent and coming from infecting strain
[m] Small sample of bacteriologically confirmed TB who had drug susceptibility test results

Estimated relative risks for different outcomes in TPT studies using rifapentine plus isoniazid[a]

				Relative risk					
	Inter-vention	Comparator	N	Active TB	Mortality	Any adverse events	Hepato-toxicity	Drug resistant TB	Completion
PLHIV ≥13 years	1HP	9H	1[b]	-0.13 (-0.52 ; 0.27)[c]	0.75 (0.42 ; 1.31)	0.79 (0.59 ; 1.04)[d]	;	0.81 (0.06 ; 11.77)[e]	1.04 (0.99 ; 1.10)
Adults with HIV	3HP	6H or 9H	2	0.73 (0.23 ; 2.3)	0.75 (0.44 ; 1.27)	0.63 (0.43 ; 0.92)	0.26 (0.12 ; 0.55)	2.00 (0.26 ; 15.44)	1.25 (1.01 ; 1.55)
	3HP	continuous H	1	1.50 (0.69 ; 3.27)	1.06 (0.47 ; 2.41)	0.20 (0.12 ; 0.32)	0.05 (0.02 ; 0.13)	1.00 (0.09 ; 10.95)	1.59 (1.40 ; 1.80)
Adults without HIV	3HP	9H	1	0.44 (0.18 ; 1.07)	0.75 (0.47 ; 1.19)	0.87 (0.73 ; 1.04)	0.16 (0.10 ; 0.27)	0.47 (0.04 ; 5.18)	1.19 (1.16 ; 1.22)
Children and adolescents	3HP	9H	1	0.13 (0.01 ; 2.54)	0.18 (0.01 ; 3.80)	0.88 (0.32 ; 2.40)	;	;	1.09 (1.03 ; 1.15)

1HP: 1-month daily rifapentine plus H; 3HP: 3-month weekly rifapentine plus H; 6H: 6-month daily H; 9H; 9-month daily H; H: isoniazid; TB: tuberculosis

a. Information on 3HP studies from the WHO report by Hamada et al. *(69)*.
b. *(70)*
c. Incidence rate ratio difference / 100 person-years between study and control
d. Serious adverse events
e. Emergence of drug resistance to rifampicin among those with confirmed TB and with DST. The RR for emergence of drug resistance to INH was 1.63 (0.17 ; 15.99). Evidence considered of very low quality because apart from restriction to PLHIV, resistance may be non-emergent and coming from infecting strain and small sample of bacteriologically confirmed TB who had drug susceptibility test results

Undesirable effects		
How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See tables above	Rifapentine has been generally well-tolerated and its use may be less problematic than rifampicin in the presence of concurrent medication like dolutegravir. The 1HP regimen has shown a good safety profile in this trial. The 3-month, weekly, HP regimen has been recommended by WHO for both low and high TB incidence settings. However, given the limited experience with the 1HP regimen (1 trial by one group), GDG members expressed some uncertainties and agreed that undesirable effects would be moderate in most settings. Amongst the concerns were the following: — Continuous isoniazid in a setting with high TB transmission among PLHIV may have a longer durability in preventive effect than a shorter regimen. In newly diagnosed PLHIV who are severely immune-compromised (particularly with CD4 <100 cells per cu mm), the recovery of the CD4 count to levels >250 per cu mm may take more than one month. When compared with longer TPT regimens it is more likely that 1HP is completed before the immune status has recovered sufficiently to protect against progression. Conversely, the CD4 count may drop fast when treatment fails and this may not be detected for several weeks. The projected decreased use of CD4 counts at HIV diagnosis or for monitoring may make it more likely to miss such situations. While the

				1HP study did not show differences in durability between 1HP and 9H it is important to note that only 2% of study participants had a CD4<100 per cu mm at baseline. — Use of HP in the presence of active TB or to treat other bacterial infections could propagate rifamycin resistance. — Concurrent use of alcohol needs to be avoided. In women on oral or injectable contraceptives the potential for drug-drug interactions needs to be considered before use. Interactions between rifapentine and methadone may occur and could be of more relevance in countries where the HIV epidemic is concentrated in opiate users. Interactions with efavirenz and dolutegravir could be a concern. More data are necessary to conclude whether dose adjustment is required when dolutegravir is used with 3HP. Even as short a duration of HP as 3 months has been associated with more rebound in viral load in people on dolutegravir several months after cessation of the LTBI regimen, although this has only been observed in two settings to date.

Certainty of evidence		
What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty in the estimates of effect (quality of evidence) was LOW for four outcomes considered CRITICAL by the GDG: incidence of active TB (inclusive of death from any cause), treatment completion, adverse events of Grade 3 or more, and mortality. The reasons why no outcome was considered of HIGH certainty were multiple: possible indirectness (trial limited to PLHIV; LTBI was not confirmed in about 80% of participants and the comparator is 9H rather than the 6H regimen more widely used in care); and other risk of bias from a single study by one trial group. Other reasons for further downgrading of the quality of evidence specific to certain outcomes were: possible misclassification when deaths from all causes are included as an endpoint and imprecision because of very small numbers for deaths from TB (LOW QUALITY; CRITICAL outcome) and for emergence of drug resistance (VERY LOW quality; IMPORTANT outcome), with the added issue for the latter outcome that resistance may have been present in the infecting strain and was not influenced by LTBI treatment received (indirectness).	The GDG concluded that the overall certainty in the evidence was LOW. Inconsistency could not be judged given that there was only a single trial; even if the study was multi-country the GDG felt that if the findings can be replicated by other studies the confidence in the estimates would increase.
Values		
Is there important uncertainty about or variation in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variation ● Possibly important uncertainty or variation ○ Probably no important uncertainty or variation ○ No important uncertainty or variation	The trial did not include an untreated group. It is expected that the benefit in the group who were TST or IGRA positive – 337 in the 1HP arm and 349 in the 9H arm – would apply to others at risk (non-inferiority of intervention regimen was shown in this group as well as overall mITT population).	The GDG considered that the shorter duration of the regimen would be welcome to most people but that there remains important uncertainty in how the regimen is best used. There are still unknowns about the value of the regimen in people without HIV There could be differences in long-term effectiveness for LTBI treatment of short duration in PLHIV with severe immunodeficiency or in settings with high TB transmission among PLHIV. Observational studies to assess long-term effectiveness would be important in this respect. Pill burden may be an issue.

Balance of effects		
Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		The GDG considered that overall the intervention would be favoured in many settings, regardless of burden/ resources. A shorter duration of LTBI treatment is likely to decrease emergence of drug resistance and adverse events. Concerns were expressed about uncertainty of effect in people not studied in the trial, such as people without HIV, women on contraceptive medicines, and children. The daily dose of rifapentine in people under 13 years is still unknown. It is also not yet clear if a change in dose of dolutegravir would be necessary when using 1HP.
Resources required		
How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ High costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	In the BRIEF TB trial (A5279), patients on the 1HP arm received 4 weeks of daily rifapentine (at a dose of 300mg daily for a weight of <35kg, 450mg daily for a weight of 35 to 45kg, and 600mg for a weight of >45 kg) plus isoniazid 300mg daily *(68)*. All treatment was self-administered. Current Global Drug Facility (GDF) cost for 28 doses of 300mg H and 600mg P is US$70. By comparison, 3HP costs about US$46 (adult >50kg), 9H US$5 (adult >50kg), 4R US$24 (adult >50kg) and 3HR between US$10 in a child (12–15kg) and US$13 in an adult (>50kg) [as in August 2019].	The GDG considered that resource use will vary depending primarily on the programmatic circumstances, such as the degree of integration with primary health care and adjustments made to accommodate the new regimen. It is important to contrast the higher costs of the medication needed for 1HP with the advantages of a shorter regimen that is more likely to be completed as prescribed, requiring less effort of the patient and health services associated with multiple visits. Reducing visits is likely to be the highest cost saving measure in both low and high resource settings. Coinciding visits with other encounters (e.g. attendance for HIV care) could save costs, but this

		could also be applicable for regimens other than 1HP. Other important future considerations for resources would be about local availability of rifapentine and the development of a low-cost fixed dose combination of HP. In common with other strategies to find people at risk and treat them for LTBI, the implementer will need to put in place appropriate resources not only to supply the medicines but also to find eligible individuals, to test them and to follow them up.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The GDG considered that given the novelty of the 1HP regimen and the lack of data on its programmatic use there remain many uncertainties about resources needed.

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies		The GDG agreed that a full cost effectiveness analysis with a longer horizon for effects and looking at different populations and settings would be important.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No specific studies or evidence	The GDG considered that this regimen is likely to be introduced without additional resources secured ahead and there is therefore a risk that its higher price could reduce access to treatment and to other health care services for all people that depend on the same resources. Given that the eligibility of the regimen still needs to be clarified the effect on equity is likely to vary. The GDG agreed that the introduction of 1HP needs to be accompanied by mobilization of appropriate resources from start to avoid shortages in different competing health care needs. On the other hand, the shorter duration of treatment could mean that more people complete their treatment and therefore when applied at large scale the overall protection of people at risk is strengthened, thus generating more public good and increasing equity.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies	The GDG considered that a shorter regimen is expected to be more acceptable to people at risk and to health services alike. Rifapentine has now been used globally and knowledge about its safety profile and interactions with other medications is well described and improving. Recent evidence that the dose of dolutegravir may not need to be changed when used with 3HP constitutes an advantage over other rifamycins. However this has

		not been validated for daily doses of rifapentine as in 1HP. The higher price of 1HP medicines could lower its acceptability compared with alternative LTBI treatments. Pill burden is substantial (3–5 tablets a day) and the advent on the market of a fixed-dose combination tablet – projected for a near future – should improve acceptability, especially if it is more affordable.

Feasibility		
Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies	In the light of the successful experience with the 3HP regimen in many settings in recent years the GDG considered that 1HP implementation would be feasible for health services and people taking it. Both component medicines are available from the Global Drug Facility catalogue. 1HP is substantially shorter than other LTBI treatments in current use and therefore its feasibility is expected to be better. If 1HP is given without a requirement for direct, in-person observation then this would make it even more feasible. Access to rifapentine may remain limited in several countries where the medicine is not registered or available through other mechanisms. Should the cost of the component medicines remain high this would influence feasibility in many parts of the world where it is needed most. However, the GDG did not consider this to be an insurmountable barrier and noted that important drops in the price of medicines for TB have occurred in the past and improved access dramatically.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variation	**Possibly important uncertainty or variation**	Probably no important uncertainty or variation	No important uncertainty or variation			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	High costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

Recommendation

A regimen with one month daily rifapentine plus isoniazid may be used as preventive treatment in people at risk of active TB
(conditional recommendation; low confidence in the estimates of effect)

Justification

When formulating this recommendation the GDG considered primarily data from the only known published study of this regimen – BRIEF-TB/A5279 – a randomized, open-label, phase 3 non-inferiority controlled trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI *(68)*. Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30); the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority as defined by the study protocol was thus shown in the mITT population; likewise non-inferiority was shown separately for the sub-groups with confirmed LTBI infection, males and females, and for those on or without ARV at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. For the discussion resource use was inferred from the costs of medicines on the Global Drug Facility catalogue needed to complete a 1HP treatment. No direct or indirect comparison of the safety and effectiveness of 1HP vs. 3HP was possible although the effects in PLHIV are comparable (see second **Table** above under the section ***Desirable effects***).

Out of the 17 GDG members, 11 expressed their views on this regimen during the GDG meeting and all were in favour of a conditional recommendation subject to specific cautions, particularly when used in people without HIV or in PLHIV who have low CD4 counts. The GDG concluded that there was low certainty that 1HP would be non-inferior to 9H when used under programmatic settings in different populations at risk. When taking into account the good safety profile of 1HP and its much shorter length when compared with other approved LTBI regimens, the GDG recommended that this regimen also be used in high TB-burden settings. The GDG considered that most people would value the shorter duration, that its implementation would be feasible, but raised concerns regarding uncertainty in resources requirements and the potential for reducing equity, leading to a conditional recommendation.

Subgroup considerations

PLHIV: The evidence underpinning the new recommendation relates primarily to PLHIV aged ≥13 years who were not pregnant or breastfeeding. The GDG thus considered that this is the population in whom there is highest certainty that the 1HP regimen would produce the benefits observed in the study. However, given the limited experience with the 1HP regimen (one trial by one group), GDG members expressed uncertainties about optimal use even among PLHIV.

Interactions with efavirenz and dolutegravir could be a concern. Despite findings reported recently from a trial suggesting few clinically significant interactions between dolutegravir and 3HP more data are needed to conclude if dose adjustment is needed or not. Even as short a duration of rifapentine as 3 months weekly dosing has been associated with increased rebound in viral load in people on dolutegravir several months after cessation of the LTBI regimen, although this has only been observed in two settings to date.

Continuous isoniazid in a setting with high TB transmission among PLHIV may have a longer durability in preventive effect than a shorter regimen. While the BRIEF-TB study did not show differences in durability between 1HP and 9H it is important to note that only 2% of study participants had a CD4<100 per cu mm at baseline. When compared with longer TPT regimens it is more likely that 1HP is completed before the immune status has sufficiently recovered or that a treatment failure is diagnosed *(68)*. In newly diagnosed PLHIV who are severely immunocompromised (particularly if CD4 <100 cells per cu mm), the recovery of the CD4 count to levels >250 cells per cu mm may take more than the month needed for 1HP. Conversely, the CD4 count may drop fast when treatment fails; this may not be detected for several weeks.

LTBI infection was only confirmed in just over 20% of trial participants. However, the trial showed non-inferiority of 1HP vs. 9H – as defined by the study protocol – both in the mITT population as well as in the subpopulation in which LTBI infection was confirmed by tests. TST or IGRA may identify PLHIV who will benefit most from TPT but testing should not be a barrier to starting LTBI treatment.

People not infected with HIV: The GDG agreed that extrapolation of efficacy and safety findings from PLHIV in the 1HP trial to all other populations who may be eligible for LTBI treatment would be acceptable given the conditional nature of the recommendation, even if the evidence to date relates solely to PLHIV from one study. When making this decision the GDG was mindful of knowledge gained from the use of 3HP in people without HIV, which does not suggest that the performance would be any different between HIV positive and negative individuals or that there will be new reactions hitherto unknown. Among people not infected with HIV the GDG highlighted infancy, early childhood and pregnancy as key situations where uncertainties are particularly relevant.

People <13 years of age: extrapolation to children aged 2-12 years may be reasonable if there are no other options although the optimal dosage of daily rifapentine in this age group is unknown. There are no or very limited data on the efficacy and safety of rifapentine in children < 2 years. This provision needs to be reviewed once results from studies of pharmacokinetics and safety in children of all ages become available in a near future.

Pregnancy: there are limited data on the efficacy and safety of rifapentine in pregnancy and therefore the use of 1HP in pregnancy would best await more data on the performance of this regimen in this subgroup. In a study of 3HP in 112 pregnant women, the rates of spontaneous abortion and of birth defects were similar to those observed in the general US population.

Other populations and drug interactions: in candidates for transplantation or anti-TNF treatment there it may be particularly important to complete LTBI treatment fast and therefore 1HP could have an advantage in this case. In homeless people and in prisoners being released from detention, given the limited opportunity to have repeat encounters, 1HP could be particularly useful. Established interactions with rifamycins with other medicines are likely to be relevant also to rifapentine. In addition to antiretroviral agents, instances where drug-drug interactions may be more relevant include concomitant use of oral or injectable contraceptive medicines and methadone in opiate users (this could be of more relevance in countries where the HIV epidemic is concentrated in opiate users). Concurrent use of alcohol needs to be avoided.

Implementation considerations
The GDG considered that the 1HP regimen could be an option to offer to people eligible for LTBI treatment regardless of TB burden setting. It should be considered not only as an alternative to 9H, which is how it was investigated in the trial, but on a broader judgement of the circumstances and other options available for people requiring LTBI treatment. Regimen choice is usually determined based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity or interaction, co-morbidity, availability and preferences. Translation of trial learnings to the programmatic realities will be critical. More advice to help guideline users in implementing the recommended treatment is available in the respective WHO operational guidance. Use of HP in the presence of active TB is highly undesirable as it promotes chronicity and emergence of drug resistance. No effort should be spared to avoid such an eventuality. As for the implementation of any TPT a robust algorithm to rule-out active disease is necessary. Rifapentine should not be used to treat other bacterial infections. There could be differences in long-term effectiveness for LTBI treatment of short duration in PLHIV with severe immunodeficiency or in settings with high TB transmission among PLHIV. Observational studies to assess long-term effectiveness would be important in this respect. The dosage recommended for 1HP should reflect the ones used in the trial: Isoniazid, 300 mg/day and Rifapentine, 600 mg/day in individuals aged ≥13 years, regardless of weight band. No data-supported recommendations exist on how to handle interruptions of 1HP, i.e. if missed doses are added at the end and after how many missed doses to start afresh. If there are contraindications to rifapentine, then an isoniazid regimen of 6 or more months would be the most likely alternative to give. If there is a contraindication for isoniazid (e.g. exposure to confirmed isoniazid monoresistant strain), then probably 4R would be the best option.

Monitoring and evaluation

The framework to monitor and evaluate the programmatic management of LTBI applies for the introduction of new regimens such as 1HP. Rifapentine has been generally well-tolerated and its use may be less problematic than rifampicin in the presence of concurrent medication like dolutegravir. The 1HP regimen has shown a good safety profile in this trial. The 3-month, weekly, HP regimen has been recommended by WHO for both low and high incidence settings.

As individuals who receive LTBI treatment do not have active disease, their risk for adverse events during treatment must be minimized. 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.

Adverse reactions that have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity) and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity) are those most likely to occur with 1HP. Monitoring should therefore focus on liver function tests, neuropathy and neutropenia. While most reactions are minor and not serious, specific attention should be paid to preventing drug-induced hepatotoxicity. There is no justification to test liver function at baseline in all people to be started on LTBI treatment, but it should be 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, clinical judgement is required to assess if benefit of TPT outweighs the risks; 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.

Monitoring for adherence to the full course of LTBI treatment and its completion are important determinants of clinical benefit to individuals and to the success of programmes. The short duration of the 1HP makes it more likely to be completed. Interventions to enhance adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. Concerns about adherence should not be a barrier to use of preventive treatment. The 2017 WHO guidelines for the treatment of drug-susceptible TB propose several interventions to support adherence in patients with active TB, which could be applied to treatment of LTBI. An electronic application for mobile phones has been created by WHO to guide national programmes on critical data to collect along the LTBI care pathway, as an accessory to monitoring and evaluation.

It would be helpful to collect information about the occurrence of active TB in people who have received 1HP or other LTBI treatment. This can be done by asking patients registered for treatment about any history of starting or completing LTBI treatment or the cross linkage of registers (e.g. LTBI registers and TB treatment registers or mortality register). In people who develop TB after 1HP treatment, or people found to have active TB well into their LTBI treatment, it would be helpful to monitor also for emergence of resistance to isoniazid and rifamycins.

In view of the decreased use of CD4 counts either at HIV diagnosis or for monitoring, there is a potential risk that PLHIV with very low immunity and who are at high risk of developing TB may have completed their 1HP well before the detection of a compromised immunity.

Research priorities

- Comparison of safety and effectiveness of 1HP with future trials and other studies performed under different conditions and populations
- More evidence on the performance of 1HP in populations who have not been studied or with limited data: children with HIV <13y; PLHIV with low CD4; children and adults without HIV; pregnant women
- Durability of effect after completion of 1HP in PLHIV and uninfected persons in areas with different intensity of TB transmission and any influence of repeated treatment courses with 1HP
- Comparison of safety, effectiveness, and cost-effectiveness of 1HP vs. 3HP
- Generation of resistance when 1HP and other LTBI regimens are used in an area
- Pharmacokinetics of rifapentine with other medicines in adults and children
- Dosage of 1HP in children (with pharmacokinetics, pharmacodynamics and modelling data), preferably to assess if flat dosing (regardless of weight band) is feasible
- Implementation research on context-specific barriers and facilitators for 1HP at programme level (acceptability, feasibility, equity, resource use)
- Cost effectiveness of the regimen under different conditions

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

Problem	Individuals with LTBI who are at high risk for active TB disease.
Option:	3-month weekly rifapentine and isoniazid (3HP).
Comparison:	Isoniazid monotherapy.
Main outcomes:	Incidence of active TB, mortality, adverse events, treatment completion, drug resistance.
Setting:	High TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000).
Perspective:	Health system and public health.

Background
Treatment of LTBI can reduce the risk for reactivation by 60–90%. WHO currently recommends two approaches for the management of LTBI, based on TB incidence and income. For high TB incidence countries, WHO recommends isoniazid preventive therapy for PLHIV and children aged < 5 years who are household contacts of people with TB. The recent WHO guidelines provide several treatment options for high- or upper-middle-income countries with low TB incidence. A previous systematic review suggested that the efficacy of the weekly regimen was similar to daily isoniazid regimens, with higher treatment completion rates and a safer profile *(69–75)*.

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't know	Uptake of LTBI treatment is still suboptimal, with only 38% of PLHIV newly enrolled in care and 7.1% of child household contacts < 5 years started on preventive treatment in 2015. A systematic review *(57)* showed that failure to complete treatment accounts for a large loss in the cascade of care for LTBI management. A previous review of LTBI treatment options *(70)* suggested that the efficacy of the weekly regimen was similar to that of daily isoniazid, with higher treatment completion rates and a safer profile. Therefore, 3HP could significantly facilitate scaling-up of LTBI treatment in high TB incidence countries.	
Balance of effects	Do the benefits outweigh the harm? ● Yes ○ No ○ Equal ○ Uncertain	We conducted a systematic review with the following subgroup analyses: adults with HIV, adults without HIV, and children and adolescents. Regardless of subgroup, there was no significant difference in the incidence of active TB in participants given 3HP and 6-months' isoniazid (6H) or 9-months' isoniazid (9H). 3HP was associated with higher completion rates (RR, 1.09–1.25) and fewer adverse events (RR, 0.63–0.88) than 6 or 9 months' isoniazid monotherapy in all subgroups. In a comparison of 3HP and continuous isoniazid, the trial showed no significant difference in TB incidence in the intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB or deaths among participants given continuous isoniazid rather than 3HP. 3HP was associated with significantly fewer adverse events than continuous isoniazid (RR 0.20, 95% CI 0.12 ; 0.32).	
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	The overall quality of the evidence was considered high for the comparison between 3HP and 6/9H in adults with HIV, moderate in adults without HIV and in children and adolescents. It was considered moderate for the comparison of 3HP with continuous isoniazid in adults with HIV.	

Values	Is there important uncertainty about or variation in how much people value the main outcomes? ○ Important uncertainty or variation ● No important uncertainty or variation	We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations *(1)*. Data were available from 142 respondents, including 10 reported as HIV-positive. The respondents were asked to rate the importance of each attribute of the LTBI treatment regimen on a five-point scale on which 5 is "very important" and 1 is "not important". More than 90% of the respondents considered the following attributes of preventive treatment to be very important or important: shorter duration, fewer side-effects, fewer visits to the clinic and fewer pills. Fewer respondents rated "less frequent intake" and "no need for DOT" as very important or important (77.3% and 74.4%, respectively). Similarly, while less than 80% of the participants rated "no need for DOT" as very important or important for their children, all the other attributes were rated as very important or important by 90–100%.	
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know	No evidence retrieved.	Implementation of 3HP would require more resources, particularly if it is to be given under DOT.
Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ● Varies ○ No included studies	In a cost–effective analysis of 3HP in the USA *(71)*, the cost was assumed to be US$6.00 per 900-mg dose of rifapentine and US$ 0.05 per dose of isoniazid. Over 20 years, 3HP given by DOT would cost the health system US$ 8861 more per TB case prevented and US$ 1879 more per quality-adjusted life year gained than 9H. From the social perspective, 3HP given by DOT was considered cost-saving. The study also found that, if adherence to self-administered 3HP is maintained at levels achieved by DOT, 3HP given by self-administration would cost less than 9H from both a health system and a social perspective.	Varies in different settings depending on cost of the drug and mode of administration (DOT or self-administration).

Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know	No evidence retrieved.	The availability of more options is generally considered to increase equity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Yes ● Varies ○ Don't know	No evidence retrieved.	Acceptability varies by risk group and setting, including mode of administration (self-administration or DOT).
Feasibility	Is the intervention feasible to implement? ○ No ○ Yes ● Varies ○ Don't know	In all the RCTs in the review, 3HP was administered under DOT. Non-inferiority of self-administered 3HP with or without text reminders for DOT was not established in the overall study population. Non-inferiority was achieved in a subgroup analysis among participants in the USA. Studies of pharmacokinetics suggest that rifapentine can be co-administered with efavirenz or raltegravir without dose adjustment. A study of the pharmacokinetics of co-administration of dolutegravir and 3HP was terminated prematurely because of the development of an influenza-like syndrome and elevated liver transaminases in two of four participants. Data on co-administration of rifapentine with other antiretroviral drugs are limited; however, as rifapentine is a potent inducer of P450 enzymes and the P-glycoprotein transport system, interactions with some antiretroviral drugs are expected. No significant interaction is expected when co-administered with abacavir, emtricitabine, tenofovir-DF, lamivudine or zidovudine. Potential interactions are expected with nevirapine and protease inhibitors. In addition, although co-administration has not been studied, rifapentine is expected to significantly reduce plasma concentrations of tenofovir alafenamide, etravirine and rilpivirine.	Feasibility depends on settings and risk groups and is mainly affected by the mode of delivery and drug interactions. The GDG noted unpublished data that suggested the effectiveness and acceptability of self-administration.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or variation**			**No important uncertainty or variation**				
Resources required	**Greater**		**Neither greater nor less**		**Less**	**Varies**	**Don't know**	
Cost–effectiveness	**Favours the comparison**		**Favours neither the intervention nor the comparison**		**Favours the intervention**	**Varies**	**No included studies**	
Equity	**Reduced**				**Increased**	**Varies**	**Don't know**	
Acceptability	**No**			**Yes**		**Varies**	**Don't know**	
Feasibility	**No**			**Yes**		**Varies**	**Don't know**	

Conclusions

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

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
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)*		
Justification	The GDG agreed unanimously that the benefits of 3HP outweigh the harm, given the similar preventive efficacy, safer profile and higher completion rate of 3HP than isoniazid monotherapy. The GDG noted that use of 3HP would require more resources, particularly if 3HP is administered by DOT. One cost-effectiveness study conducted in the USA suggested that 3HP may be more cost-saving than 9-months isoniazid. There was consensus in the GDG that the cost-effectiveness of 3HP depends mainly on the cost of the drug and mode of administration, which would affect the costs to patients and health systems. There was consensus in the GDG that the acceptability of 3HP varies by risk group and setting, due mainly to the mode of administration (self-administration or DOT). The GDG considered that adding 3HP as an alternative to isoniazid would provide more options and hence increase equity.		
Subgroup considerations	The GDG recognized the lack of data on use of 3HP in pregnant women and children < 2 years and stressed the need for data on these populations.		
Implementation considerations	The GDG noted that 3HP can be self-administered. Evidence from an RCT suggests that adherence to self-administered treatment of 3HP is not inferior to DOT. There is little further evidence on use of the 3-month regimen of weekly rifapentine plus isoniazid. The GDG noted that a requirement for DOT could be a significant barrier to the implementation. 3HP should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions. The GDG noted that the 3HP can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics. Administration of rifapentine with raltegravir was found to be safe and well tolerated. Rifapentine-containing regimens should not be administered with dolutegravir until more information becomes available. The GDG urged further studies on the pharmacokinetics of 3HP with a variety of drugs, particularly ART.		
Monitoring and evaluation	The GDG stressed the importance of recording and reporting on the provision and completion of TPT according to standardized indicators, in order to monitor progress in implementation.		
Research priorities	• Value of self-administration of 3HP. • Studies of pharmacokinetics with a variety of drugs, particularly ART. • Use of 3HP in pregnant women and children < 2 years old.		

GRADE tables

Question: Should a 3-month regimen of weekly rifapentine plus isoniazid be offered as an alternative regimen to daily isoniazid monotherapy for treatment of TB infection in high TB incidence countries?

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

Overall quality: high

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

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

From references *72* and *73*

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

Question: Should a 3-month regimen of weekly rifapentine plus isoniazid be offered as an alternative regimen to daily isoniazid monotherapy for treatment of TB infection in high TB incidence countries?

Population: Adults with HIV
Comparison: Continuous isoniazid monotherapy

Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month weekly RPT+isoniazid	Continuous isoniazid	Relative (95% CI)	Absolute (95% CI)		
Active TB												
1	RCT	Not serious	Not serious	Not serious	Serious[a]	None	24/328 (7.3%)	8/164 (4.9%)	RR 1.500 (0.689–3.265)	24 more per 1000 (from 15 fewer to 110 more)	Moderate	Critical
All-cause mortality												
1	RCT	Not serious	Not serious	Not serious	Serious[a]	None	17/328 (5.2%)	8/164 (4.9%)	RR 1.063 (0.468–2.410)	3 more per 1000 (from 26 fewer to 69 more)	Moderate	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month weekly RPT+isoniazid	Continuous isoniazid	Relative (95% CI)	Absolute (95% CI)		
Any adverse events (grade III or IV)												
1	RCT	Serious[b]	Not serious	Not serious	Not serious	None	21/328 (6.4%)	53/164 (32.3%)	RR 0.198 (0.124–0.317)	259 fewer per 1000 (from 221 to 283 fewer)	Moderate	Critical
Hepatotoxicity												
1	RCT	Not serious[c]	Not serious	Not serious	Not serious	None	5/328 (1.5%)	46/164 (28.0%)	RR 0.054 (0.022–0.134)	265 fewer per 1000 (from 243 to 274 fewer)	High	Critical
Drug-resistant TB												
1	RCT	Not serious	Not serious	Not serious	Very serious[d]	None	2/328 (0.6%)	1/164 (0.6%)	RR 1.000 (0.091–10.948)	0 fewer per 1000 (from 6 fewer to 61 more)	Low	Important
Completion rate												
1	RCT	Not serious	Not serious	Not serious	Not serious	None	314/328 (95.7%)	99/164 (60.4%)	RR 1.586 (1.398–1.799)	354 more per 1000 (from 240 to 482 more)	High	Critical

From reference *72*

[a] 95% CIs of both relative and absolute effect indicate appreciable benefit and harm with 3HP.

[b] The trial was open-label, which may have introduced bias in ascertainment of adverse events.

[c] 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.

[d] Very low event rates. The upper limits of 95% CIs of both relative and absolute effect indicate appreciable harm with 3-month weekly RPT and isoniazid. Downgraded by two levels.

Question: Should a 3-month regimen of weekly rifapentine plus isoniazid be offered as an alternative regimen to daily isoniazid monotherapy for treatment of TB infection in high TB incidence countries?

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

Overall quality: moderate

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

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

From reference *74*

[a] No study provided a 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 the effect of RPT/isoniazid as compared with isoniazid monotherapy. Downgraded by one level.

[b] Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.

[c] Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. Not downgraded.

[d] The open-label design of the trial may have introduced ascertainment bias. Downgraded by one level.

[e] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

Question: Should a 3-month regimen of weekly rifapentine plus isoniazid be offered as an alternative regimen to daily isoniazid monotherapy for treatment of TB infection in high TB incidence countries?

Population: Children and adolescents
Comparison: 6 or 9 months' isoniazid

Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month RPT+isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
Active TB												
1	RCT	Not serious	Not serious	Serious[a]	Not serious[b]	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007–2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	Moderate	Critical
All-cause mortality												
1	RCT	Not serious	Not serious	Serious[a]	Not serious[c]	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009–3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	Moderate	Important

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

From reference *75*

[a] No study provided a comparison with 6 months of isoniazid. Although the trial was conducted in low TB incidence countries, this is unlikely to affect the relative effect of RPT/isoniazid as compared with isoniazid monotherapy. Downgraded by one level.

[b] Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.

[c] Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. Not downgraded.

[d] The open-label design of the trial may have introduced ascertainment bias.

[e] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

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

The Guideline Development Group noted the lack of evidence and therefore decided not to update the existing recommendation. There is therefore no Evidence to Decision table.

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

Should 6 months of levofloxacin vs. other regimen or no TPT be used for people in contact with MDR/RR-TB?

Population:	People in contact with MDR/RR-TB
Intervention:	6 months of levofloxacin
Comparison:	Other regimen or no TPT
Main outcomes:	TB incidence; death; adverse events; adverse events of any grade leading to treatment discontinuation; treatment completion; emergence of additional FQ resistance in TB strains; emergence of additional FQ resistance in microbiome other than TB (e.g. gut flora)
Setting:	Two RCTs of 6 months of LFX in contacts of MDR-TB in South Africa (TB CHAMP) and Viet Nam (V-QUIN). We used results from a pooled analysis of data for individual study participants to express estimates of effect, rather than the Bayesian analysis, which largely mirrored the results from the frequentist approach

Assessment

Problem		
Is the problem a priority?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Drug-resistant tuberculosis is one of the most prominent causes of morbidity and mortality from an antimicrobial resistant organism. Globally, there were an estimated 410,000 incident cases of MDR/RR-TB in 2022. An estimated 160,000 deaths due to MDR/RR-TB occurred in 2022 *(76)*. With recent advances in therapeutics and increased global access to more effective medication, treatment success has improved over time. However it still remains lower than for rifampicin-susceptible TB (63% for people starting treatment in 2021). People with MDR/RR-TB may infect other individuals. It is thus important to take all measures possible to lower the risk of secondary cases of MDR/RR-TB. This includes the use of appropriate TPT with regimens of proven effectiveness.	Key considerations expressed by GDG members when deciding that MDR/RR-TB is a priority problem and that measures to prevent it, like TPT, were crucial were as follows: The 2020 TPT guidelines include a recommendation for TPT of contacts of MDR/RR-TB that is conditional and based on evidence of very low certainty. The recommendation is not specific to any regimen and its implementation since first published in 2017 has been poor. Now that trial-based evidence for a defined treatment regimen has become available it becomes more important to review the new evidence to assess the efficacy of this new regimen to prevent this formidable public health problem.

Desirable effects

How substantial are the desirable anticipated effects?

Judgement

- ○ Trivial
- ○ Small
- ● Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Research evidence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with other regimen or no TPT	Risk with 6 months of levofloxacin			
TB incidence assessed with: bacteriologically confirmed or clinically defined TB, TB-related death at 54 weeks	Study population		RR 0.38 (0.17 to 0.86)	2963 (2 RCTs)	High
	14 per 1000	**5 per 1000** (2 to 12)			
Treatment completion assessed with: opposite of discontinuation	Study population		RR 0.88 (0.85 to 0.92)	2963 (2 RCTs)	High
	829 per 1000	**730 per 1000** (705 to 763)			
Treatment completion assessed with: 80% or more of doses taken by 6 months	Study population		RR 0.88 (0.85 to 0.91)[a]	2928 (2 RCTs)	High
	850 per 1000	**748 per 1000** (723 to 774)			

[a] Treatment completion in the levofloxacin arm was 86% in TB CHAMP (placebo arm: 86%) and 70% in V-QUIN (placebo arm: 85%) – RRs 1.00 [95% CI 0.95 to 1.06] and 0.83 [0.79 to 0.87] respectively

A systematic review of studies published between June 2016 and September 2023 identified three observational studies that assessed TB prevention (reduction in incidence) with FQ (alone or in combination with other TB drugs), and one assessed prevention of TB with isoniazid. All four were observational studies with substantial risk of bias, notably selection bias. The three studies with FQ did not detect any reduction in TB incidence with FQ use, compared to no TPT. The study of isoniazid estimated a significant reduction with isoniazid, although this effect was similar in those who took less than 3 months isoniazid (1/77 incident TB cases, aHR 0.31 [95% CI, 0.03–1.98]) and those who took isoniazid for more than 3 months (1/127 incident TB cases, aHR, 0.17 [95% CI, 0.02–1.34]). An IPD of 496,527 contacts identified 8,952 contacts of MDR/RR-TB of whom 722 received isoniazid and 4,223 received no TPT. Reasons for initiating or not initiating isoniazid, and duration of isoniazid taken were not available. After matching (using propensity scores) for measured potential confounders the estimated effect was a 65% reduction in TB with 6 months isoniazid compared to no TPT. Completion of therapy, concomitant exposure, drug sensitivity patterns in the untreated group developing disease were not available.

The results from the systematic review and from the isoniazid IPD could not be summarized in the GRADE table.

Additional considerations

Key considerations expressed by GDG members when making a judgement of MODERATE desirable effects were as follows:

The efficacy of levofloxacin in the trails was similar to the one observed in other studies of TPT, although uncertainty was expressed regarding the durability of effect.

The risk for MDR-TB in a person exposed and the seriousness of the disease, with its high lethality, more complicated treatment and likelihood to relapse unless properly treated, are important considerations, regardless of the background risk of MDR-TB in different contexts. Any intervention that can reduce this risk would be welcome.

There is an observation that the two outcomes presented here – TB incidence and TPT completion – are going in opposite directions, making it difficult to judge, as the judgements for incidence may be different than for treatment completion.

							It was noted that the number needed to treat was different in V-QUIN (193 [98-5495]) and TB CHAMP (56 [30-389]). The decision was made on the pooled data because separation by adults and children would reduce precision and lower the quality of evidence. This will be developed further in the Subgroup considerations. Separately from this, the GDG noted that the findings reported from the isoniazid IPD on effectiveness, survival and completion were inconclusive, and that this study did not fully address the PICO question (effects of levofloxacin vs. other or no TPT).

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement

- ○ Large
- ○ Moderate
- ○ Small
- ○ Trivial
- ● Varies
- ○ Don't know

Research evidence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with other regimen or no TPT	Risk with 6 months of levofloxacin			
Death (Death) assessed with: any cause	Study population 3 per 1000	**3 per 1000** (1 to 13)	**RR 1.26** (0.34 to 4.68)	2963 (2 RCTs)	Low[a]
Adverse events (AE) assessed with: Grade 3 or above at least possibly related to study drug (TB CHAMP; under 18y) follow-up: 6 months plus 21 days	Study population 17 per 1000	**9 per 1000** (3 to 29)	**RR 0.53** (0.16 to 1.70)	921 (1 RCT)	Moderate[b]
Adverse events (AE Grade 3 or above) assessed with: Grade 3 or above at least possibly related to study drug (V-QUIN; 97% of participants >14y) follow-up: 6 months plus 30 days	Study population 2 per 1000	**11 per 1000** (2 to 50)	**RR 5.26** (1.16 to 23.95)	1922 (1 RCT)	High
Adverse events of any grade leading to treatment discontinuation (AE leading to discontinuation) follow-up: 6 months plus 21 or 30 days	Study population 8 per 1000	**53 per 1000** (29 to 98)	**RR 6.32** (3.43 to 11.63)	2843 (2 RCTs)	High
Emergence of additional fluoroquinolone resistance in TB strains (Fluoroquine resistance (TB))	In none of 8 strains from index-incident pairs in the V-QUIN trial that were tested with whole genome sequencing was additional resistance to levofloxacin or other antimicrobials detected[c]		–	8 (2 RCTs)[d]	Very low[c,e,f]

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

Additional considerations

Key considerations expressed by GDG members when making a judgement of VARIES for undesirable effects were as follows:

There was an important difference in the risk of adverse events between children (trivial) and adults (moderate), with very good tolerance in children and much less tolerability with increasing age, that has likely contributed to lower adherence to TPT in adults. Some forms of toxicity should not be discounted given that the regimen would be rolled out for use in programmatic settings.

The results on emergence of resistance were inconclusive, although these were not CRITICAL outcomes.

Separately from this, the GDG noted that there were no findings reported from the isoniazid IPD on adverse events, and that this study did not fully address the PICO question (effects of levofloxacin vs. other or no TPT).

A systematic review of studies published between June 2016 and September 2023 identified five observational studies that assessed adverse events with FQ (alone or in combination with other TB drugs). All were observational studies with substantial risk of bias, notably selection bias. Detection, judgement of severity, and attribution were not blinded, potentially leading to ascertainment bias. FQ monotherapy (i.e. LFX, OFX, or MFX alone) was observed in three studies to be generally safe, with some mild or moderate drug-related AEs in children, but no grade 3/4 or serious AE. In a study evaluating FQ with a companion drug (ETH/EMB), the regimen had a higher observed rate of grade 1/2 drug-related AEs compared to the studies with FQ monotherapy (ETH+FQ had a significantly higher AE rate than EMB), but no serious AEs were reported and AEs were not associated with treatment discontinuation. FQ with PZA was found to have very low tolerability in a small study among inmate contacts by Bedini et al 2016 (7/12 contacts discontinued treatment due to AEs). An IPD of 496,527 contacts identified 8,952 contacts of MDR/RR-TB of whom 722 received isoniazid and 4,223 received no TPT. Completion of therapy, and adverse events in the treated group were not available (likewise in the Huang et al study from the systematic review). The results from the systematic review and from the isoniazid IPD could not be summarized in the GRADE table. (See Annex 5 for more details.)

The GDG scored the two outcomes on emergence of additional resistance as IMPORTANT rather than CRITICAL. While the two trials collected data on the emergence of additional fluoroquinolone resistance to TB strains and other flora, results of drug-susceptibility testing or whole genome sequence were incomplete at the time of the GDG meeting. Only one outcome from 8 TB strains tested (2 of which from the levofloxacin arm) in the V-QUIN trial was included in the evidence summary table, which showed no additional resistance acquired. The effects of levofloxacin on resistance in other microbiome could not be satisfactorily quantified for inclusion in the evidence table. Results suggested, amongst others, a drop in taxonomic diversity of faecal bacterial populations at the end of levofloxacin therapy compared with baseline, and which persisted after post-treatment cessation; increased abundance of genes associated with fluoroquinolone resistance, as well as a gene commonly associated with extended spectrum beta-lactamase (ESBL); and a loss of fluoroquinolone susceptible methicillin-resistant Staphylococcus aureus (MRSA) isolates from nasal swabs. An increase in quinolone resistance of E. coli / K. pneumoniae in stool was noted from baseline to week 16 in both arms of the TB CHAMP but was higher in the levofloxacin arm; although these were matched samples the data had not been analyzed at participant level by the time of the GDG meeting. It was not possible to compare these effects with those caused by other TPT regimens or to appreciate the long term clinical significance of these findings.

Certainty of evidence		
What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Certainty is judged to be HIGH for TB incidence, treatment completion, adverse events GRADE 3 or above at least possibly associated with study drug in adults, MODERATE for adverse events GRADE 3 or above at least possibly associated with study drug in children, and LOW for death (all CRITICAL outcomes). It was considered VERY LOW for the emergence of additional fluoroquinolone resistance in TB strains and was not estimable for the emergence of additional fluoroquinolone resistance in microbiome other than TB (eg gut flora) (both IMPORTANT outcomes). Evidence from studies identified by the systematic review was considered of very low certainty for efficacy, and low certainty for adverse events (all studies were observational). The low incidence of Grade 3-4 adverse events, as well as low occurrence of discontinuation of FQ TPT due to adverse events, in adults and children, from observational studies is consistent with evidence from the trials. Evidence from an analysis of child contacts exposed to MDR/RR-TB index patients, of whom 722 received isoniazid and 4,223 received no TPT, suggests a significant reduction of incident TB disease with isoniazid. However, this evidence is considered very low certainty due to substantial potential for selection bias, uncertainty in completion as well as follow-up, and uncertainty if the effect seen was related to prior infection or concurrent exposure to drug-susceptible TB strains. In addition, this study did not answer the PICO which was to compare the effect of FQ with any other treatment, such as isoniazid, or no treatment.	Key considerations expressed by GDG members when making a judgement of MODERATE certainty of the evidence of effects were as follows: The two trials were well conducted, large and independently showed very similar estimates of reduction in TB incidence in two different settings with populations of different characteristics. It was acknowledged that we are unlikely to get such high quality evidence from trials of fluoroquinolone as a TPT for MDR-TB in a foreseeable future (PHOENIX trial is using 26-weeks of delamanid and is expected to be completed at the end of 2026). However, uncertainties were expressed given the serious or very serious imprecision on the adverse events and the fact that there are only two trials. It was highlighted that there may be difficulties to standardize some of the endpoints between the two trials. Effects from pooled estimates were felt to be less robust. The evidence for emergence of additional resistance to fluoroquinolones was considered uncertain. Separately from this, the GDG noted a very low certainty in the estimates reported from the systematic review and the isoniazid IPD.

Values		
Is there important uncertainty about or variation in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variation ○ Possibly important uncertainty or variation ● Probably no important uncertainty or variation ○ No important uncertainty or variation	Evidence from the systematic review (2 published studies on acceptance to start MDR TPT, 2 published studies on willingness to take hypothetical MDR TPT, 1 published study on acceptability of a novel child friendly LFX formulation, and 1 published explorative qualitative study included in the systematic review) suggested that OVERALL acceptability of MDR TPT to prevent incident TB disease was high. However, based on the qualitative acceptability study (among 36 HHCs from 5 countries), there is indication of possibly important uncertainty or variation. Although the sample size was still relatively small, this study that included people with a wide range of TB and MDR knowledge and experience, as well as with very different socioeconomic and cultural backgrounds, found meaningful differences in TPT acceptability. For example, although most people valued a lowered risk of developing MDR-TB, some refused to accept any risk of serious adverse events due to TPT, which overrode any value they placed in avoiding MDR-TB. The study suggests that in the case where there is an absence of trained HCWs or researchers recruiting them, and taking the time to explain TPT to them, the value for prevention is quite low, the understanding of the severity/risk of MDR also seems very low, and the value in one's present health is very high by contrast. Arguably, this is a very important variation in values that could really affect real-world uptake of MDR TPT.	Key considerations expressed by GDG members when making a judgement of PROBABLY NO IMPORTANT UNCERTAINTY OR Variation in values were as follows: The values are likely to depend on how much people being offered fluoroquinolone TPT are well informed about the efficacy and downsides of TPT, and the seriousness of MDR-TB. In all situations safety is paramount particularly for a person who is not ill. There were some financial, emotional and psychological factors that played into adherence. They may be overcome with education but still important. Acceptance for people who started TPT was quite high and more than is seen with comparable interventions under programmatic settings. However, the evidence reviewed is from small samples so maybe not generalisable

Balance of effects		
Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The reduction of MDR-TB incidence with the intervention of LFX by 60% in adults and children is offset only by mild Grade 1-2 AEs. Both desirable and undesirable effect estimates are derived from two RCTs that are judged to be of high quality overall, and the ascertainment of these outcomes was also free of bias and there was sufficient precision that we can be reasonably certain of these effects. The estimates of low rates of Grade 1-2 adverse events and very low rates of Grade 3-4 adverse events are supported by observational studies found in the systematic review, although it was not possible to estimate a pooled rate of mild or severe adverse events in the review due to heterogeneity of interventions reported, and definitions of adverse events used.	Key considerations expressed by GDG members when making a judgement of PROBABLY FAVOURS THE INTERVENTION for the balance of effects were as follows: It is noted that, based on the evidence presented to the GDG, the benefits outweigh the risks, especially in children. To a large extent the adverse events were mild and self-limiting. Although not critical for this assessment, emergence of other resistance is important and there is uncertainty about how it could reduce the potential benefit from the intervention. The evidence reviewed was incomplete and the implications of the effects reported for the overall population and for the individual in the long term are unknown. It was highlighted that the use of fluoroquinolone as a TPT for MDR-TB should be considered as an appropriate use of antimicrobial agents, unlike inappropriate use that is more likely to generate avoidable resistance. It is noted that the effects of using levofloxacin at a wide scale in a population is unknown.

Resources required		
How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ High costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Based on a self-administered questionnaire survey among national TB programme (NTP) managers of 30 high-burden MDR-TB countries, of whom 18 (60%) responded, 7 of 18 respondents stated that the cost of additional resource requirements may be a barrier to implementation, with some mentioning specifically the concurrent need for drug-susceptibility testing, screening, monitoring, and follow-up in the programme as well as the already limited human resources and budgets within programmes. The paediatric dispersible formulation of levofloxacin is much more expensive than the adult formulation (a tenfold difference per mg at current GDF prices – approx. US$0.12/100mg tablet vs. US$0.03/250mg tablet respectively).	Key considerations expressed by GDG members when making a judgement of MODERATE COSTS for the resources required were as follows: The cost of levofloxacin, a generic medication in wide use, is relatively low when compared with other TPT or no TPT. However, the health system costs to deliver the overall intervention may entail additional investments in programmatic components that are weak, such as screening and identifying contacts, drug-susceptibility testing, monitoring for adverse events, capacity building to improve the skills of healthcare workers, engaging communities, increasing treatment literacy, and providing social support. There is no reason to consider that these costs will be excessive. Investments may generate gains in the long term and the need for additional expenditure should not stop programmes from doing what is necessary to prevent and care for MDR-TB. It was also noted that overall the burden of MDR-TB patients is relatively low compared with drug-susceptible TB.

		Those not procuring through the Global Drug Facility mechanism may face a higher price for a product of guaranteed quality, as well as differences in costs if the 750mg formulation is used instead of the 250mg. However, this variation in the exact per patient budget impact may not have had a major influence in the NTP survey responses.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	A single self-administered questionnaire and completion rate of only 60%. The pricing of the Global Drug Facility medications is standardized for all countries eligible.	Key considerations expressed by GDG members when making a judgement of LOW for the certainty of evidence of required resources were that there was only one survey reviewed and that there was no evidence on costs for implementation.

Cost effectiveness		
Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ No included studies	A systematic review of studies published between June 2016 and September 2023 identified one cost-effectiveness study of TB prevention (reduction in incidence) with FQ for MDR contacts. According to a high-quality CEA study cost-effectiveness was highest when implementing levofloxacin/moxifloxacin for children <5 and children <15 with HIV (ICER, US$738 per DALY) but it averted fewer total deaths and years of life lost than providing LFX/MFX for all children <15 (870 deaths averted compared to 1240 respectively). The cost-effectiveness of LFX/MFX decreased in countries with higher FQ resistance, with greater number of contacts under the age of 15 years needing to be treated per TB episode averted. This analysis was very recently updated using the efficacy estimates from the two trials (TB CHAMP, and V-QUIN), and results were very similar (unpublished data provided by J Seddon), (see Annex 5). A sub-study conducted by the V-QUIN investigators estimated that for every 1000 adult MDR contacts provided LFX as TPT, compared to monitoring only would result in: (i) A total health system cost saving of US$2,091, and a total health gain of 40.96 QALYs. LFX TPT would also result in prevention of 0.56 MDR-TB cases and 2.66 deaths. A sub-study conducted by the TB CHAMP investigators estimated that for every 1000 children offered TPT compared to a monitoring only scenario where baseline (untreated) risk of developing MDR disease is 2.5%: (i) A total health saving of $11.3 million, and a total health gain of 30 healthy life years (QALYs); (ii) TPT would also result in prevention of 11 non-severe MDRTB cases, 4 severe MDR-TB cases, and 1 death.	Key considerations expressed by GDG members when making a judgement of FAVOURS THE INTERVENTION for cost-effectiveness were as follows: Cost-effectiveness favours the intervention as it saves money rather than generating costs. While the paediatric formulation is more expensive, the cost-effectiveness analysis still finds it cost-effective, and it is noted that children have one of the highest risks of progression to TB disease from infection. It is noted that the cost-effectiveness sub-analysis presented here is based on a setting where the risk of progressing to TB disease is 2.5%; in areas where the risk is lower, the analysis may not have the same findings.

Equity		
What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Based on a self-administered survey questionnaire among NTP managers of 30 high-burden MDR-TB countries, of whom 18 (60%) responded, overall equity was expected to increase, from the perspective of the managers, for contacts through the avoidance of TB disease incidence. However, 6 NTPs mentioned that certain remote areas may not have an adequate supply of LFX. Additionally, 11 NTPs mentioned increased out-of-pocket spending for contacts, with 2 stating the need for health insurance to cover TPT to ensure equity. Importantly, interviews with contacts themselves in the qualitative acceptability study (36 HHCs from 5 countries) suggested that those with little income, unstable or no employment, little or no social support, will likely NOT be able to accept and complete a 6-month TPT regimen that will require at least monthly check-ups, and maybe some mild side effects, especially at the beginning of treatment that could impact their daily activities and responsibilities (see Annex 5). Also, caregivers for the MDR index patients or other contacts within the household are unlikely to be able to start/accept TPT as well, unless they have access to improved socioeconomic support systems. Hence findings from this qualitative study suggest that equity may be reduced by the introduction of TPT for MDR contacts, unless this is accompanied by improved social and financial support	Key considerations expressed by GDG members when making a judgement of PROBABLY INCREASED for equity were as follows: Some people might benefit more from levofloxacin than others. From a drug perspective there is more equity because we can prevent TB in more people, given the efficacy of the drug. Equity may increase if services are provided to contacts at high risk of drug-resistant TB and who are generally marginalised and who have difficulty to access services. From a model of care perspective, equity is more likely in situations where drug costs are covered by the public health system. Otherwise, the intervention might shift cost to the affected person and lead to out of pocket payments that can reduce equity. So, it is important to think about improving models of care to protect the person needing the drug from incurring cost from the drug and other healthcare system components. In situations where the health system covers the expenditure for levofloxacin, another consideration is about the opportunity cost of investing in levofloxacin as a TPT for MDR-TB. Will the cost of treatment be deducted from another important programmatic component, like TPT for non-MDR-TB or the treatment of people with MDR/RR-TB?

Acceptability		
Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A systematic review of studies published between June 2016 and September 2023 identified five observational quantitative studies that assessed acceptance in starting TPT when offered, willingness to take a hypothetical MDR TPT regimen, and acceptability (ability and willingness to use TPT as directed) of TB prevention treatment with FQ, and a sixth qualitative study conducted in South Africa as a sub-study of the TB CHAMP trial (refer to Annex 5 for studies mentioned in this section). Two studies indicated an 80% acceptance rate among caregivers, for their children to be started on TPT, and among adolescents and adult contacts. Two studies indicated 90% willingness by caregivers and 70% among adults to take TPT for MDR-TB, and one study indicated high levels of acceptability by caregivers administering a novel dispersible child-friendly formulation of LFX to their children. The published qualitative study found an overall high acceptability of LFX among caregivers of children as well but found that there were some pragmatic difficulties around the financial and care burden of providing TPT to their children, especially for caregivers undergoing treatment for TB disease themselves (which was a motivator for accepting treatment but limited capacity to care for children). Greater social support led to greater capability to ensure adherence to treatment for both caregivers and children. A qualitative study conducted among 36 MDR-TB contacts in 5 countries (Georgia, India, Indonesia, South Africa, and Viet Nam) concluded that: TPT for MDR was acceptable and of high social value among participants in all 5 settings. The most acceptable TPT regimen would have a high degree of effectiveness in preventing MDR/RR-TB, no risk of side effects that are permanent or that could interfere with daily activities, few pills and a short duration, low socioeconomic cost, and minimal clinical follow-up visits. A retrospective quantitative sub-study conducted by the V-QUIN investigators examined acceptability among a randomly selected sample of 240 participants in the V-QUIN trial (about equal numbers took placebo, and LFX). They found no major differences in ratings of medication taste, size, frequency of preventative treatment between arms. Of all participants less than 20% rated the duration ideal, and almost one third rated the duration as too long. Acceptability was somewhat worse in those who did NOT complete study drug. Only a minority of participants would take the treatment again or would recommend to others. A prospective quantitative sub-study among all participants in the TB Champ trial examined acceptability on every treatment phase visit and found that the taste of levofloxacin was disliked by children more than placebo, but the children in both arms adapted to the taste over the course of treatment. Caregivers found it more difficult to administer levofloxacin than placebo, but overall, more than 95% of caregivers reported NO difficulty in giving levofloxacin. Overall, the investigators concluded that acceptability was reasonable, but noted an association between poor acceptability and poor adherence. In addition, a semi-structured interview was conducted to evaluate caregiver experience of administering novel child-friendly levofloxacin formulation in 10 child/caregiver dyads on the side of TB-CHAMP. There was a relatively high overall acceptability. One major motivator was the caregivers' own experiences with MDR-TB illness, and treatment. Pragmatic difficulties were expressed around financial and care burden on the household due to TPT. Challenges were exacerbated for caregivers who were on treatment for their own MDR-TB disease, limiting their capacity to care for their children. Caregivers who received greater social support reported better capability for them and their children to adhere to treatment.	Key considerations expressed by GDG members when making a judgement of PROBABLY YES for acceptability were as follows: In the survey of national TB programme managers many stated that they would accept the recommendation only if it is strong. The 6-month duration of treatment may be a challenge although this is the same as the minimum duration of isoniazid that is still one of the most widely used TPT regimens worldwide. Six months has also been the duration of standard treatment for drug-susceptible TB and for the new BPaL(M) regimen for MDR/RR-TB. However, a shorter TPT would be preferred in future. Other factors such as cost, administration issues and the taste of medication were also mentioned as challenges. The high frequency of adverse events in in adults in particular was highlighted. Providing clear information on benefits and risk and a supporting environment to caregivers and beneficiaries is likely to improve acceptability: people's perceptions of the effectiveness and value of TPT are important.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Based on a self-administered survey questionnaire among NTP managers of 30 high-burden MDR-TB countries, of whom 18 (60%) responded, in the case of a strong WHO recommendation, an additional 8 countries (apart from the 6 that were already implementing 6LFX) were ready to implement LFX programme-wide. A conditional recommendation made it less likely for 7 NTPs. All managers anticipated that drug storage, transportation, and distribution was sustainable. However, the need for additional resources (DST, monitoring and follow-up) were raised as concerns/barriers to implementation by 7 of 18 managers.	Key considerations expressed by GDG members when making a judgement of YES for feasibility were as follows: There is already a WHO recommendation for the use of TPT in MDR-TB which has been implemented to some degree despite it being conditional, with levofloxacin being one of the options proposed. Feasibility will depend upon additional resources being available to implement the intervention properly, such as drug-susceptibility testing of the presumed source case and testing for TB infection (in the TB-CHAMP trial a positive tests for infection was not required in most individuals; in the V-QUIN trial adults could participate if TST positive) and chest X-ray (done for participants in both trials). Levofloxacin is widely available as a generic drug in both adult and paediatric formulations.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		**Varies**	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variation	Possibly important uncertainty or variation	**Probably no important uncertainty or variation**	No important uncertainty or variation			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	High costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☐	☒

Conclusions

Recommendation

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

Justification

The GDG reached a decision on the strength of the recommendation after a vote in which 11 members out of the 14 present (79%) agreed to a STRONG recommendation, based on MODERATE certainty in the estimate of effects. The main factors that determined this decision were the following:

- the potency of the intervention to achieve its intended effect
- its overall good tolerability, particularly in younger people
- its cost-effectiveness
- the probability that it would increase equity
- a consideration that it would be generally acceptable and feasible

The GDG noted that there is insufficient evidence to make a recommendation on the use of isoniazid as a TPT for MDR/RR-TB. The main considerations leading to this decision were the following:

- the data that were reviewed do not fully address the PICO (ie, data do not compare the effect of isoniazid against levofloxacin or other regimens)
- all studies that were available were observational in nature
- in those offered isoniazid the uptake was low (<20% overall in the individual participant study) and the reasons for not taking it were not known
- there was incomplete information on whether people not taking isoniazid received any other TPT
- the duration of isoniazid use and its dose were not known
- there was no information on whether people who developed TB despite isoniazid had drug-susceptible TB or MDR-TB

Subgroup considerations

Children and adolescents: levofloxacin can be used in children and adolescents, in whom completion and tolerability in the TB CHAMP trial was much better overall. There is no requirement for testing for TB infection before starting levofloxacin in children who are contacts of MDR-TB. Although there has been concern about the use of fluoroquinolones in children because of retardation of cartilage development in juvenile animals exposed to these agents *(77)*, similar effects have not been demonstrated in humans *(78,79)*. While the effects of fluoroquinolones on bone and cartilage in animals have not been observed in humans, available data and infant follow-up times are limited. There remain nonetheless safety concerns associated with prolonged use of fluoroquinolones in humans *(80,81)*.

Pregnancy and breastfeeding: TPT with levofloxacin in pregnancy will require a risk to benefit assessment and an informed choice sought from the pregnant woman on whether or not to take TPT or to defer to the end of pregnancy. The advice should depend on the circumstances (e.g. first trimester vs. later). There is no evidence to support the prolongation of levofloxacin beyond 6 months. Pregnancy increases the risk of progressing from infection to disease and the risk of poor maternal and foetal outcomes should TB disease ensue. MDR-TB in pregnancy is a serious condition and some of the drugs used to treat MDR-TB are or may be toxic to the foetus. Observations from studies in animal exposed to levofloxacin have limited its use in pregnancy. However, one meta-analysis of observational studies with 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women *(82)*. Levofloxacin concentrations in breastmilk appear to be far lower than the infant dose and would not be expected to cause adverse effects in breastfed infants *(83)*. Its use should not be suspended during breastfeeding.

Contraindication: levofloxacin should not be given to people who are allergic to fluoroquinolone, who have another contraindication to the class of drugs or who have a potential for a drug-drug interaction. It should be discontinued if the person develops a serious or severe adverse drug reaction to it. In people exposed to a source case with documented resistance to fluoroquinolones another TPT option (see also in Implementation considerations).

HIV infection: levofloxacin can be used regardless of HIV status. In people with HIV exposed to MDR-TB there is no need for a test of infection before starting levofloxacin.

Implementation considerations

The strong recommendation reflects the GDG opinion that the benefits of levofloxacin outweigh the potential harm in most people who are eligible. Health programmes and clinicians should strive to ensure eligibility for its use and maximise the likelihood that treatment is completed as expected. TPT with levofloxacin should also consider factors such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability and the individual's preferences.

People receiving TPT should also be supported through access to advice on treatment and management of adverse events at their encounters with the health services. Contacts should be followed up regardless of whether TPT was completed or not. Individuals receiving treatment, clinicians providing treatment and programme managers would prefer shorter to longer regimens. The GDG noted that the 6-month duration of levofloxacin appear long to the patient and caregivers, in comparison to shorter TPT regimens of 4 or 12 week duration that are however only available for prevention of drug-susceptible TB (duration of treatment with delamanid is also for 6 months in the only other ongoing major trial investigating MDR-TB TPT).

Obtaining a positive test for TB infection before starting TPT for MDR-TB is not required in child contacts and people with immunocompromising conditions. In other populations this would be desirable but not mandatory. The unavailability of testing should not be a barrier to provide TPT to individuals who are at risk. Screening of all the household and other close contacts for co-prevalent TB disease will be important.

Levofloxacin is the preferred choice of fluoroquinolone to give as TPT, given that both trials used this agent. While there are no comparable data to support the use of alternatives, moxifloxacin can be used if levofloxacin is not available. Drug-susceptibility testing of the source case strain would be an important additional piece of information, especially in situations where fluoroquinolone resistance is known to be high. If the strain of the presumed source shows resistance to these medicines, other second line drugs can be used as TPT based on the best available information on the drug susceptibility profile of the presumed source. In this case, the certainty of the effectiveness of TPT is much lower than for the use of levofloxacin. Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case isoniazid may be considered effective.

The GDG considered that levofloxacin could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure the treatment is given correctly without creating inequities, and that TB disease can be excluded reliably before the initiation of treatment. As for other TPT, the GDG noted that treatment can be self-administered and that a requirement for a direct observation could be a significant barrier to implementation. Digital adherence technologies (e.g., electronic medication monitors) may be used to support patients but studies of their use for TPT are sparse.

The model by which care is delivered is important to enhance uptake of the recommendation. If the health system covers the cost of treatment and care then equity could increase. Caregivers should understand why the recommendation is strong in the presence of moderate certainty in the evidence: that high quality evidence from RCTs in different settings showed similar efficacy for a regimen that safely lowers the risk for a life-threatening, infectious condition that is difficult to treat. Engaging stakeholders in the community is important as for other TPT efforts to address the constraints in implementation.

The dosing schedule for LFX in children, adolescents and adults in the guideline have been updated in the operational handbook that accompanies following a discussion with the Technical Advisory Group for dosing of TB medicines in early 2024.

Monitoring and evaluation

Most individuals who receive TPT are healthy and adverse reactions to treatment are likely to influence their likelihood of completing it. Drug-related toxicity should therefore be minimized. Levofloxacin is generally safe and well tolerated but adverse reactions have been reported. Caregivers should be aware of the spectrum of adverse reactions associated with their use so that they can elicit them and take action rapidly. Most reactions are minor and self-limiting, but severe or serious reactions may occur less commonly. Adverse events should be monitored according to the WHO framework for monitoring and managing the safety of medicines against TB disease *(84)*, and pharmacovigilance systems should be strengthened to gather further information about adverse reactions from the long term use of fluoroquinolones. Consideration should also be given to potential interactions with other medicines that the patient may be taking (such as antacids, sucralfate, metal cations, multivitamins, oral antihypoglycaemic agents, warfarin, theophylline, cyclosporine and non-steroidal anti-inflammatory agents). People on levofloxacin should also be advised to contact their healthcare provider at any time if they become aware of symptoms such as inflamed or torn tendons, muscle pain or weakness, joint pain or swelling, difficulty walking, paraesthesiae, burning pain, fatigue, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell. If a healthcare provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately. This is one of the critical areas for frontline healthcare workers and students to receive training on.

Individuals on TPT should be monitored routinely at monthly encounters with healthcare providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Monitoring the adherence to TPT and ensuring its completion are conducive to clinical benefit. Digital adherence technologies (e.g., electronic medication monitors) have been used to support patients complete curative TB treatment and may have a role in TPT as well.

There is no evidence that the use of fluoroquinolones as TPT has led to the emergence of drug-resistant TB strains in a community. TB disease must be excluded before TPT is initiated, and regular follow-up is required to ensure early identification of people who develop TB disease while receiving TPT. The GDG reiterated that strict clinical observation and close monitoring for TB disease, based on sound clinical practice and national guidelines, is required for at least 1 year after MDR-TB exposure, regardless of whether TPT was taken or not. In people who develop TB after or well into a TPT it would be important to test for emergence of resistance.

There is concern that the expansion of use of fluoroquinolones for TB and other infectious conditions could enhance the emergence of fluoroquinolone-resistant strains and compromise the efficacy of levofloxacin as a TPT. National surveillance systems for anti-TB drug resistance needs to be strengthened in countries scaling up fluroquinolone-containing TB treatment regimens.

Coverage of contact investigation and TPT among contacts and people with HIV are among the top 10 core indicators for monitoring implementation of the End TB Strategy. The use of levofloxacin as TPT for MDR-TB can be integrated in this indicator. National TB and HIV programmes report data yearly to WHO and UNAIDS on progress in TPT scale up in target populations. PMTPT should include monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems. Standardized indicators should be measured to regularly inform decision-making for programme implementation. Some may require changes to national regulations or health policies (e.g. making TB infection a notifiable condition or mandating a reporting 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. Electronic applications for mobile phones and other devices can be used to guide national programmes on critical data to collect along the TB preventive care pathway, as an accessory to monitoring and evaluation (e.g. PREVENT TB app, https://www.who.int/activities/preventing-tb#app). Such application could also be helpful to collect information about the occurrence of TB disease in people who have received TPT with levofloxacin. This can be done by asking patients registered for TB treatment about any history of starting or completing TPT or the cross linkage of registers (e.g. registers of people given TPT compared with TB treatment or mortality registers).

(More detail is provided in the updated operational handbook that WHO is releasing with these guidelines)

Research priorities
The evidence reviewed ahead of the current update exposed research gaps in the area of TPT for MDR/RR-TB. Continued research remains important for several aspects of the TPT. Information to fill these gaps needs to be collected in part through special trials and in part as implementation research under programmatic conditions.
The new, strong recommendation by WHO for levofloxacin as TPT for MDR/RR-TB should not signal no further need to study this subject, or create ethical impediments for ongoing or future trials exploring other regimens as TPT.
It will be critical to develop TPT regimens for MDR-TB that are shorter than 6 months and with good safety profile in childhood, pregnancy and in the presence of co-morbidities or risk of drug-drug interactions. Pregnancy should not be an absolute exclusion criterion in such studies.
The long-term efficacy of TPT regimens for MDR-TB would be important to understand especially in settings with high risk of MDR-TB re-exposure. Monitoring the efficacy of fluoroquinolones and other TPT in areas with high levels of resistance in TB strains to the medications used as TPT will be useful. Exploring regimens that remain effective in the presence of fluoroquinolone-resistant TB strains will be important in areas of high fluoroquinolone resistance.
Programme-based surveillance and studies of special design are needed to monitor for the emergence of clinically-relevant resistance to fluoroquinolones in TB and other bacterial strains and to other the medicines used at large scale for TPT.
The collection of programmatic data on adverse events and maternal and pregnancy outcomes, inclusive of post-natal follow-up of the child, could supplement current knowledge about the safety of levofloxacin TPT when used in pregnancy and breast-feeding.
Studies about the effectiveness of context-specific interventions to enhance adherence and completion of treatment, such as self-administration with and without the use of digital adherence technologies, will be helpful. Implementation research on context-specific barriers and facilitators is needed for TPT to MDR-TB, to explore dimensions for which evidence is often sparse, such as acceptability, feasibility, equity and resource use.
Continued epidemiological research is needed to determine the burden of TB infection in specific geographical settings and risk groups, and risk of progression, as a basis for nationally and locally tailored interventions, including integrated community-based approaches.
Research is also needed on service delivery models for TPT, to lower costs, enhance equity and to optimize the follow-up of people exposed to MDR-TB, whether or not they received fluoroquinolones, in terms of duration, monitoring approaches, and frequency of visits. Future evidence could guide better how to optimise contact tracing strategies in households as well as how to deliver public health interventions for common modifiable risk of affected people, such as use of tobacco, drugs and alcohol.

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Annex 5. Summary of unpublished studies (PICO 10)

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

Tuberculosis Child Multidrug-Resistant Preventive Therapy Trial (TB CHAMP): Efficacy and safety of levofloxacin preventive treatment in child and adolescent HHCs of multidrug-resistant tuberculosis (MDR-TB). Author: Anneke Hesseling[7]

V-QUIN MDR-TB prevention study: Levofloxacin versus placebo for the treatment of tuberculosis infection among contacts of patients with MDR-TB. Author: Greg Fox[8]

Methods

TB CHAMP: A phase III cluster double-blind group randomized placebo-controlled trial to assess the efficacy and safety of a 6-month regimen of daily levofloxacin (6Lfx) as TB preventive treatment (TPT) in child contacts of patients with MDR-TB. The trial protocol was registered at ISRCTN registry (ISRCTN92634082; https://doi.org/10.1186/ISRCTN92634082)

V-QUIN: Double-blind parallel group randomized controlled trial to compare a 6-month regimen of daily levofloxacin (6Lfx) with placebo for the treatment of TBI. The objective was to determine the efficacy of levofloxacin (Lfx) in preventing the development of bacteriologically confirmed TB. The trial was registered prospectively with the Australian and New Zealand Clinical Trials Registry (ACTRN 12616000215426; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817)

Objectives

TB CHAMP

Primary objective: To assess whether Lfx given daily for 24 weeks (15–20 mg/kg) is effective in preventing TB in child HHCs (HHC) of adults with MDR-TB

Secondary objectives

1. Does Lfx have acceptable toxicity and tolerability in children?
2. Is adherence similar in the study arms?
3. Is Lfx cost-effective and acceptable to prevent MDR-TB in child HHC?
4. Are there differences in Lfx resistance between study arms for children who develop incident TB?

V-QUIN

Primary objective: To evaluate the effectiveness of Lfx given for 6 months rather than placebo in prevention of TB disease among HHC of patients with MDR/RR-TB who have TB infection.

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[7] Stellenbosch University, Cape Town, South Africa

[8] University of Sydney, Sydney, Australia

Secondary objectives: evaluation of:

1. incidence of grade 3–4 adverse events
2. mortality
3. adherence to treatment (completion of > 80% of doses in < 270 days)
4. cost-effectiveness
5. acquired resistance to Lfx

Intervention

TB CHAMP: comparison of 24 weeks of daily Lfx (15–20mg/kg, maximum 750 mg) to 24 weeks of daily placebo.

V-QUIN: 180 days of self-administered oral Lfx, or an indistinguishable placebo, once per day. Tablets were distributed every 4 weeks, and a pill count performed at each visit. The daily dosing range was 10–15 mg/kg for adults, and 15–20 mg/kg for children, with a maximum dose of 750 mg.

Population eligibility

TB CHAMP

The study was completed in urban and rural settings of five provinces in South Africa, a high-incidence country for TB, TB/HIV and MDR/RR-TB. Children were considered eligible for enrolment if they fulfilled all the inclusion criteria and none of the exclusion criteria, as defined below.

Criteria for inclusion of a child or adolescent participant

- child or adolescent < 18 years who is a HHC of an adult MDR-TB index case (as stated under adult MDR-TB eligibility criteria) (up to version 2.0 protocol, only children aged < 5 years were eligible)
- primary residence in the household of the adult MDR-TB index patient or any contact resulting in significant exposure of the child
- consent from the parent or legal guardian for HIV testing
- consent from the parent or legal guardian for enrolment
- assent obtained from any child or adolescent ≥ 7 years
- if > 5 years and < 18 years of age, the child or adolescent must have a positive IGRA (Quantiferon-Gold Plus, Qiagen) test before enrolment, unless HIV positive. Children < 5 years eligible regardless of IGRA status. All HIV-positive children < 18 years of age are eligible regardless of IGRA test status.

Criteria for exclusion of a child or adolescent participant

- TB disease at enrolment
- currently on INH or a fluoroquinoline (e.g. Lfx, moxifloxacin, ofloxacin or ciprofloxacin) for ≥ 14 days. TPT may be interrupted provided that the child or adolescent participant is recruited into the study as soon as possible.
- treated for TB in the previous 12 months
- known concurrent exposure to an INH-susceptible (including rifampicin [RIF] mono-resistant) index case
- weight < 3.0 kg
- positive pregnancy test at enrolment (For women who become pregnant on study, continuation on study treatment is allowed.)
- ≤ 6 months post-partum

Inclusion criteria for adult index patients

- age ≥ 18 years

- bacteriologically confirmed pulmonary TB diagnosed from a sputum sample, treatment for MDR-TB started within the preceding 6 months
- genotypic or phenotypic resistance to INH and rifampin (RIF). If only tested by Xpert MTB/RIF or MTB/RIF Ultra or other approved molecular tests e.g. line probe assay, the index case can be included if RIF-resistant, without other confirmed DST; i.e. confirmation of both RIF and INH resistance not required.
- written informed consent from the index case (or a close relative if the index case is deceased prior to the completion of screening)
- at least 1 HHC below the age of 18 years reported to have been residing in the same household as the adult index case in the previous 6 months

Exclusion criteria for adult index patients

- MDR-TB with confirmation of genotypic or phenotypic resistance to fluoroquinolones (FQs) (version 3.0 protocol)

V-QUIN

The study was conducted in Viet Nam, which is among the high-incidence countries for TB and MDR/RR-TB. Participants were recruited in urban and rural settings in 10 provinces. The study sites delivered standard programmatic management of drug-resistant TB within the National Tuberculosis Programme (NTP).

Inclusion criteria for randomization

- all ages (participants < 15 years were enrolled only during the final 6 months of recruitment in conformity with the requirements of the local institutional review board)
- either:
  (1) tuberculin skin test (TST) positive, defined as either (a) ≥ 10 mm first reading; (b) new TST conversion on the second reading (≥ 10 mm at second reading and an increase of ≥ 6 mm at the second reading over the first reading, OR
  (2) any TST size if known HIV positive or severely malnourished (body mass index < 16 kg/m^2).

Exclusion criteria

- current TB disease
- known to be pregnant
- unable to take oral medication
- body weight < 3 kg
- unwilling or unable to participate in follow-up
- currently breastfeeding
- known allergy to FQ antibiotics or history of severe tendinopathy related to FQs
- currently taking another medication reported to increase the cardiac QTc interval
- documented previous treatment for MDR-TB
- documented treatment with antibiotics that are active against MDR-TB in the previous months
- prior severe blistering reaction to tuberculin
- end-stage liver failure (class Child-Pugh C)
- dialysis-dependent chronic kidney disease
- a baseline liver function test, aspartate or alanine aminotransferase over three times the upper limit of normal
- kidney tests show end-stage kidney disease (estimated glomerular filtration rate < 20 mL/min)
- platelet count < 50 × 10^9 cells/L
- baseline electrocardiogram shows a QT segment > 450 ms (adults)

Randomization and trial procedure

TB CHAMP: All eligible children in a household were treated with the same drug (either all Lfx or all placebo). Households were randomized (allocated by chance) to be in the Lfx or the placebo group. Allocation conducted by computer, and households had an equal chance of being in either group. In this "double blind" study, neither the children (or their family) nor the researchers knew whether the tablets each child took were Lfx or placebo.

A CXR (anteroposterior and lateral images) was completed at baseline and, if any evidence of TB on the CXR or if the child had any symptoms or signs suggestive of TB, they underwent sampling for mycobacterial evaluation. IGRA and HIV testing were done in all children at baseline, and the result was required before enrolment of children aged 5–17 years. A pregnancy test was performed at baseline for all female participants who had begun menstruation. A full blood count, alanine transaminase and bilirubin were collected at baseline in all children. Children were followed at 4, 8, 12, 16, 24, 48 and 72 weeks and at additional unscheduled visits as clinically indicated. At each visit, children were assessed clinically for symptoms and signs of TB, new exposure to TB and for evidence of any adverse events due to the medication. Adherence to medication was quantified by pill returns and counts, treatment diaries and questionnaires. Weight and height were measured at each visit, all concomitant medications documented, and any outpatient or inpatient health-care visits were recorded. The dose of medication was adjusted monthly as necessary. A CXR (AP and lateral) was done at baseline and at 12 and 48 weeks and at any time of clinical concern. Two respiratory samples were collected for mycobacterial evaluation if the child had any symptoms or signs suggestive of TB or if they had an abnormal CXR. Sampling for presumed pulmonary TB consisted of induced sputum or gastric aspiration in children < 5 years, while children aged ≥ 5 years were encouraged to produce an expectorated sputum sample. Samples for presumed extrapulmonary TB were taken according to the site of disease. All samples were examined by smear microscopy, Xpert MTB/RIF Ultra and mycobacterial culture. Drug susceptibility (first- and second-line drugs) was tested in all mycobacterial isolates by genotypic and phenotypic methods.

V-QUIN: Participants were assigned to parallel groups in a 1:1 ratio in a permuted block design with varying block size, stratified by province. The allocation sequence was concealed before randomization. Within a household, participants were placed on the same regimen if enrolled within 90 days of one another to avoid a contamination effect.

During the 6-month treatment period, participants attended a clinic monthly to assess toxicity and support adherence. Patients were also telephoned between scheduled visits, every 2 weeks. After treatment, participants attended follow-up sessions for assessment of incident TB with a symptom screen and CXR at 6, 12, 18, 24 and 30 months. In addition, patients were assessed by telephone interviews for symptoms every 3 months during the follow-up. Throughout follow-up, participants with symptoms consistent with TB or CXR abnormalities were asked to produce three sputum samples for Xpert MTB/RIF and liquid culture. After the 30-month follow-up period (up to 134 weeks), participants were asked to produce a single sputum sample for Xpert MTB/RIF testing. Those diagnosed with TB disease were treated with a standard first- or second-line regimen according to national guidelines and the drug susceptibility profile – if available.

Outcome ascertainment

TB CHAMP: The primary end-point for efficacy was incident TB disease (bacteriologically confirmed or clinically diagnosed) or death from TB at the 48-week study visit after randomization, with a 6-week window allowed, i.e. through week 54. The prespecified main secondary end-point for safety was adverse events (AEs) grade ≥ 3 assessed by the site investigator as at least possibly associated with the study treatment. Other secondary end-points included:

- TB disease by 72 weeks
- all-cause mortality

- any AEs grade ≥ 3 from starting study treatment up to 30 days after the last study drug dose
- serious AEs up to 30 days after the last study drug dose
- discontinuation of study treatment due to AE(s)
- selected pre-defined AEs, from starting treatment up to 30 days after the last study drug dose unless stated otherwise (arthritis, arthralgia, tendinopathy during overall study follow-up, peripheral neuropathy, central nervous system effects, severe rash/cutaneous reaction and drug related fever)
- treatment adherence.

Incident TB and cause of death were adjudicated by an independent end-point review committee who were unaware of the randomized treatment allocation, according to all available clinical, radiological, microbiological and molecular data according to standard international consensus case definitions.

V-QUIN: Outcomes were reported for each participant. The primary study end-point was bacteriologically confirmed TB, defined as a positive identification of *M. tuberculosis* by culture or a molecular WHO-recommended rapid diagnostic in a close contact with clinical and/or radiological evidence of TB disease. The primary outcome was assigned by an expert clinical panel that was blinded to group allocation.

Secondary end-points included all forms of TB (bacteriologically confirmed or clinically probable), completion of therapy, treatment discontinuation due to an adverse event, grade 3 or 4 adverse events, death from any cause except violence, accident or acquired resistance to FQs in comparison with the index isolate. Completion of treatment was defined as having taken at least 80% of doses within 270 days after starting therapy. Secondary safety outcomes were assigned by an expert clinical panel that was blinded to group allocation.

Statistical methods

TB CHAMP

Sample size

In the original sample size calculations, a 50% reduction in TB disease incidence was assumed by 48 weeks (i.e. 50% efficacy of Lfx), from 7% in the control group to 3.5% in the Lfx group. The originally calculated sample size was 1556 participants, which would provide 80% power for the study at a 5% two-sided significance level, assuming an average of two participants enrolled per household; the household intra-class correlation was 0.10, with 10% loss to follow-up. In May 2019, after discussion with the Trial Steering Committee and the Independent Data Monitoring Committee, the target sample size was reduced to 1009 according to an assumed efficacy of 60% for Lfx (with other assumptions remaining unchanged). This assumption was considered to be in line with the results of the meta-analysis by Marks et al. (2017, doi:10.1093/cid/cix208).

Statistical analyses

- primary efficacy analysis included all randomized participants except for any late screening failures due to TB at baseline (mITT population);
- pre-defined ± 6-week window allowed for study visit at 48 weeks, with follow-up time censored at 54 weeks;
- Cox regression used to estimate hazard ratio of time to TB end-point with Lfx compared with placebo, accounting for household clustering and adjusting for site and age group;
- safety analyses included all randomized participants who had received at least one dose of study drug and comparison of time to first event between treatment arms; and
- IPD and Bayesian analysis: TB-CHAMP and V-QUIN

V-QUIN

Sample size

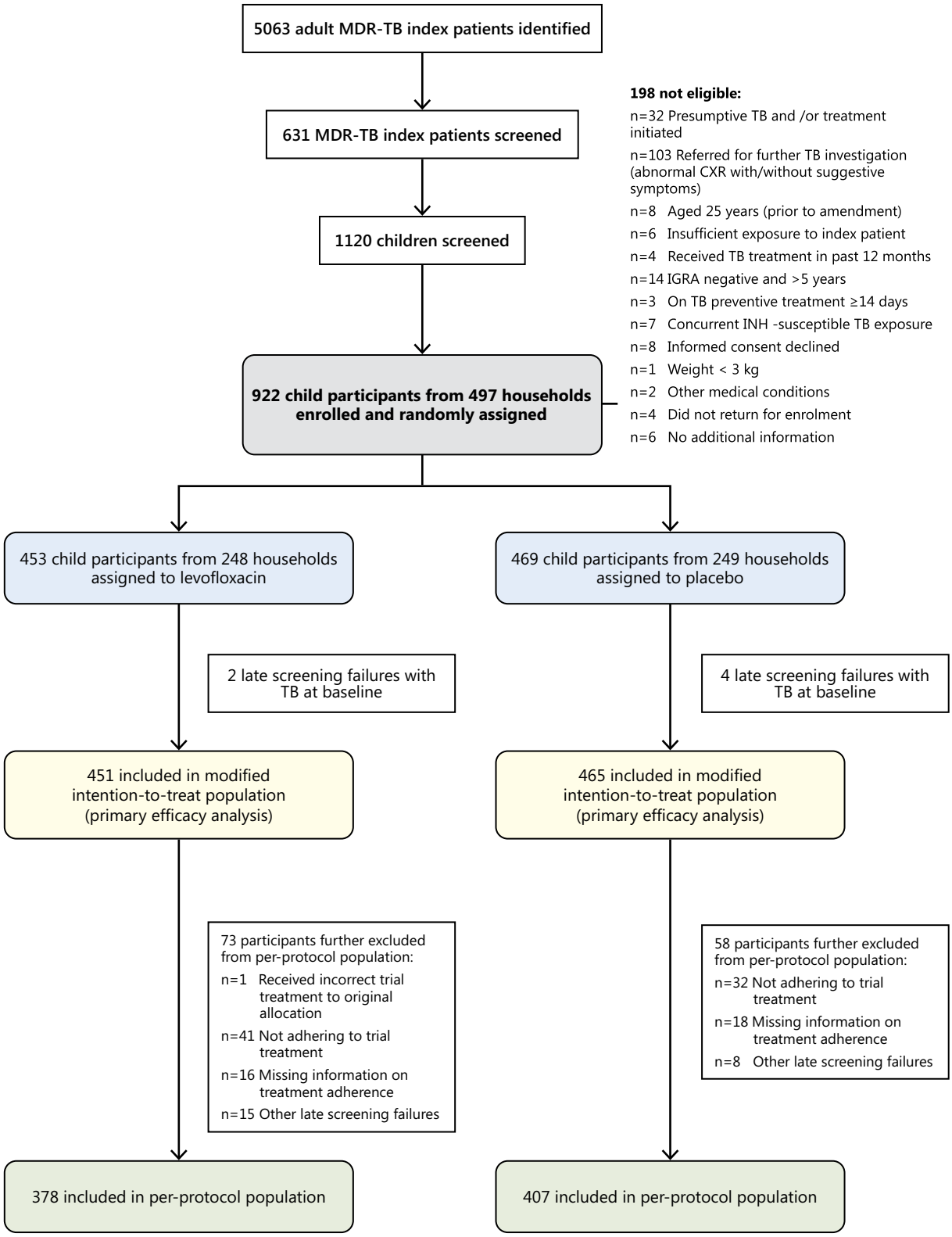
The risk of incident TB in the placebo group was expected to be 3% during the follow-up period, with an expected reduction in incident TB with Lfx by 70% in the treatment group, based on estimates of isoniazid efficacy in DS-TB. The sample size was increased to allow for 17% FQ resistance among patients with RR/MDR-TB in Viet Nam, a 10% drop-out rate and a design effect of 1.04 at district level and 1.07 at household level. To determine superiority, the required sample size was 1003 per arm on the basis of a two-sided alpha level of 0.05 and a power of 80%, allowing for clustering at district and household levels.

Statistical analyses

- The analysis was conducted according to a plan. Group assignment was blinded until analyses were complete. The primary analysis included the intention-to-treat (ITT) population. ITT analyses were also performed on the secondary (composite) outcomes of bacteriologically confirmed or clinically probable TB and all-cause mortality. The per-protocol population included all randomized participants who completed at least 80% of their assigned treatment. The mITT population excluded contacts of patients with RIF-susceptible TB and participants who did not start therapy.
- An interim safety analysis was performed to assess the rate of grade 3 and 4 adverse events after 600 contacts had completed 6 months of therapy. A pre-specified secondary Bayesian analysis was conducted to evaluate the incidence of confirmed or clinically probable TB at 54 weeks.
- The incidence rate ratios and 95% confidence intervals (95% CIs) were estimated in a marginal Poisson regression model fitted via generalized estimating equations.
- A complete case analysis was performed for the primary and secondary analyses.

Fig. A5.1. CONSORT diagram

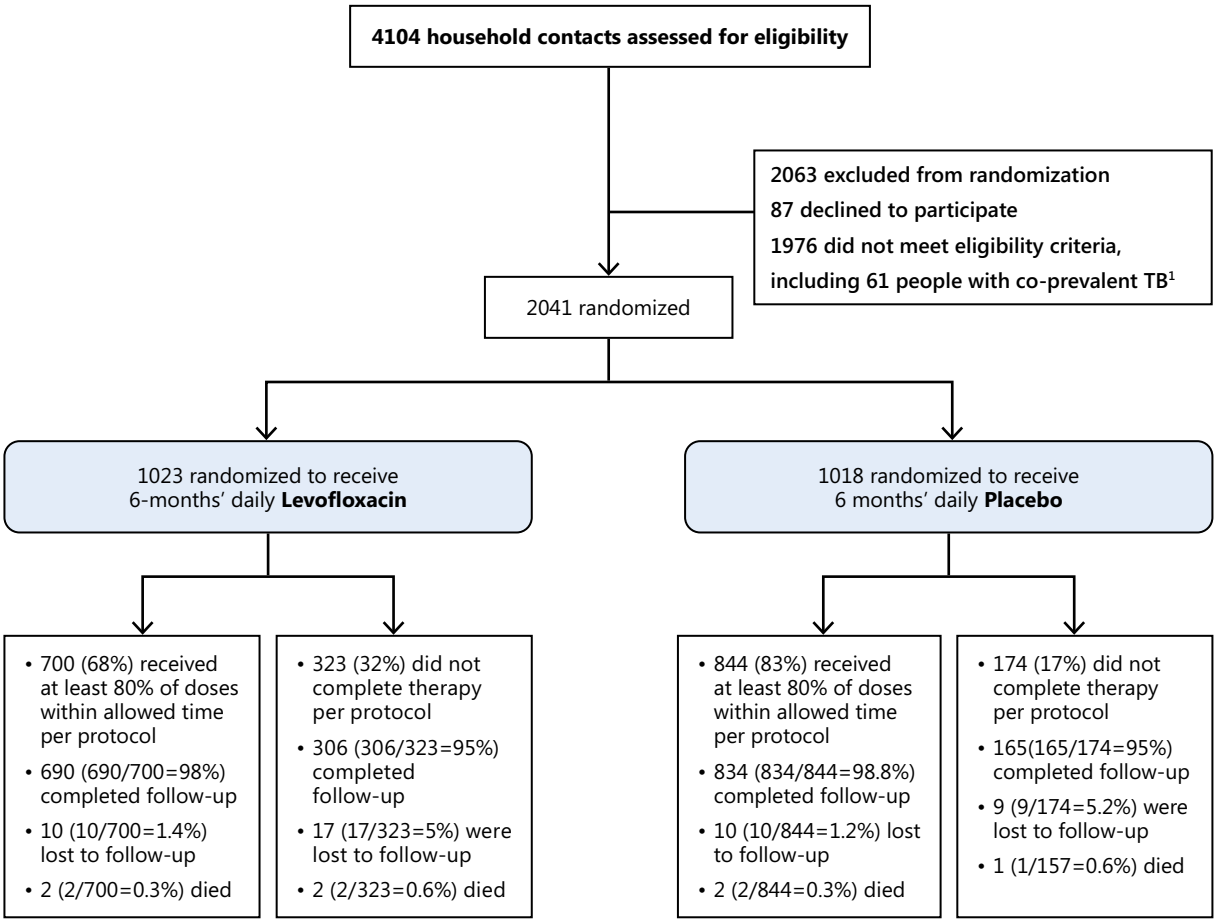
TB CHAMP: Overview of enrolment, randomization and analysis of multi-drug-resistant tuberculosis child HHCs



MDR, multidrug-resistant; TB, tuberculosis; CXR, chest x-ray; IGRA, interferon-γ release assay; INH, isoniazid

Of the 5063 adult index patients identified, 631 were screened. Index patients were ineligible for screening because: the study team was unable to establish contact with the index patient, the index patient had died or moved, the index patient was < 18 years of age, the index patient had RIF-mono-resistant TB, had been on treatment for more than 6 months, had non-pulmonary TB, or no children < 5 years were reported to be living in the household during the past 6 months.

Fig. A5.2. V-QUIN: recruitment of HHCs



[1] *Co-prevalent TB 4 people with bacteriologically confirmed and 17 people with clinically diagnosed TB*

Results

TB CHAMP

Table A5.1. Baseline characteristics of randomized child participants (N=922)

Participants randomized (N)		Levofloxacin 453 (100%)	Placebo 469 (100%)	Overall 922 (100%)
Female		240 (53%)	228 (49%)	468 (51%)
Age (years)	Median (IQR) years	3.0 (1.4, 4.3)	2.6 (1.3–4.1)	2.8 (1.3–4.2)
	<1	85 (19%)	83 (18%)	168 (18%)
	1–<3	140 (31%)	175 (37%)	315 (34%)
	3–<5	180 (40%)	176 (38%)	356 (39%)
	5–<10	18 (4%)	17 (4%)	35 (4%)
	10–<15	20 (4%)	13 (3%)	33 (4%)
	15–<18	10 (2%)	5 (1%)	15 (2%)
Black race		362 (80%)	381 (81%)	743 (81%)
BCG vaccinated		423 (94%)	442 (95%)	865 (94%)
HIV-positive		10 (2%)	9 (2%)	19 (2%)
HIV-exposed uninfected		153 (34%)	160 (34%)	313 (34%)
Currently on TB preventive treatment		9 (2%)	6 (1%)	15 (2%)
Weight-for-age Z score, median (IQR)		-0.4 (-1.2–0.3)	-0.4 (-1.2–0.4)	-0.4 (-1.2–0.3)

Children and adolescents aged 5–17 years were required to be IGRA-positive or living with HIV to be eligible

BCG, bacille Calmette-Guérin; IQR, interquartile range

Table A5.2. Primary efficacy analysis – mITT population

mITT population	Levofloxacin	Placebo	Total
All participants	451	465	916
Participants with ethics review committee adjudicated TB endpoint during overall study follow-up	7 (1.6%)	14 (3.0%)	21
Confirmed TB	3	7	10
Unconfirmed TB	4	7	11
Primary efficacy analysis			
Participants with TB end-point by 48 weeks[a]	5 (1.1%)	12 (2.6%)	17
Confirmed TB	3	7	10
Unconfirmed TB	2	5	7
Hazard ratio (95% CI), Levofloxacin vs placebo[b]	0.44 (0.15 ; 1.25)		
P	0.121		

[a] Allowing for pre-defined ± 6–week window at study visit at 48 weeks

[b] Hazard ratio estimated by adjusting for site, age group and allowing for household clustering

mITT, modified intention-to-treat

Table A5.3. Primary safety analysis[a]

Participants	Levofloxacin	Placebo	Total
All participants receiving ≥ 1 study treatment doses	452	469	921
Grade ≥ 3 adverse events at least possibly associated with study drug			
Number of events	5	8	13
Participants with ≥ 1 event(s)	4 (0.9%)	8 (1.7%)	12
Hazard ratio (95% CI), Levofloxacin vs placebo[b]	0.52 (0.16 ; 1.71), *P* = 0.285		

[a] Analyses based on time to first event.

[b] Hazard ratio estimated adjusting for site, age group and allowing for household clustering.

Table A5.4. All-cause mortality

Number of deaths	Weeks between randomization and death	Age (years)	Cause of death[a]	Attributable to TB[a]	Related to study drug
Levofloxacin					
1	38.9	11 months	Cardiac arrest	Unrelated or unlikely	Unrelated
Placebo					
1	11.3	12 months	Viral pneumonia	Unrelated or unlikely	Unlikely

[a] As adjudicated by the ERC.

Results V-QUIN

Table A5.5. Participant characteristics

Characteristic	Levofloxacin	Placebo	Total
	n (%)	n (%)	n (%)
Total	1023 (100%)	1018 (100%)	2041 (100%)
Age, median age (years, IQR)	41 (28, 52)	39 (28, 53)	40 (28, 52)
< 15	27 (2.6%)	33 (3.2%)	60 (2.9%)
15–29	262 (25.6%)	253 (24.9%)	515 (25.2%)
30–44	290 (28.4%)	324 (31.8%)	614 (30.1%)
45–59	329 (32.2%)	277 (27.2%)	606 (29.7%)
≥ 60	115 (11.2%)	131 (12.9%)	246 (12.1%)
Male gender	374 (36.6%)	361 (35.5%)	735 (36.0%)
Time per day with index case, median h (IQR)	5 (2, 10)	5 (2, 11)	5 (2, 10)
History of TB	56 (5.5%)	50 (4.9%)	106 (5.2%)
Comorbidities			
Diabetes	38 (3.7%)	38 (3.7%)	76 (3.7%)
Chronic kidney disease	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hepatitis B	12 (1.2%)	22 (2.2%)	34 (1.7%)
Hepatitis C	1 (0.1%)	1 (0.1%)	2 (0.1%)
HIV positive	2 (0.2%)	6 (0.6%)	8 (0.4%)
Chronic lung disease	12 (1.2%	8 (0.8%)	20 (1.0%)
TST status			
TST positive	920 (89.9%)	907 (89.1%)	1827 (89.5%)
TST conversion	101 (9.9%)	108 (10.6%)	209 (10.2%)
TST negative and HIV positive	1 (0.1%)	1 (0.1%)	2 (0.1%)
TST negative and body mass index < 16 kg/m^2	1 (0.1%)	2 (0.2%)	3 (0.2%)

IQR, interquartile range; TST, Tuberculin skin test

Table A5.6. Incidence of TB among all participants

Characteristic	Levofloxacin	Levofloxacin-incidence per 100 person-years	Placebo	Placebo incidence per 100 person-years	Incidence rate ratio (95% CI)	*P value*
Intention to treat population	n = 1023		n = 1018			
Completed 30 months follow-up or reached a trial end-point, n (%)	996 (97.4%)	-	999 (98.1%)	-	-	-
Total follow-up, person-years	2586.1	-	2564.6	-	-	-
Bacteriologically confirmed[a], n	6	0.232	11	0.429	0.55 (0.19 ; 1.62)	0.278
Clinically diagnosed only, n	1	0.039	2	0.078	0.49 (0.045 ; 5.46)	0.566
Either bacteriologically confirmed or clinical TB, n (%)	7	0.271	13	0.507	0.54 (0.20 ; 1.46)	0.226

Characteristic	Levofloxacin	Levofloxacin-incidence per 100 person-years	Placebo	Placebo incidence per 100 person-years	Incidence rate ratio (95% CI)	*P value*
Per protocol population	n=700		N=844			
Total follow-up, person-years	1783.7	-	2145.3	-	-	-
Bacteriologically confirmed, n	3	0.168	6	0.280	0.60 (0.15 ; 2.39)	0.474
Clinically diagnosed only, n	0	0.000	1	0.047	Not estimated	-
Bacteriologically confirmed or clinical TB, n	3	0.168	7	0.326	0.52 (0.14 ; 1.99)	0.338

[a] Primary effectiveness outcome

Table A5.7. Adverse events (intention to treat population), per subject

Variable	Levofloxacin (N=1023)	Placebo (N=1018)	Risk difference	*P value*
Participants who took at least one dose of study drug	960 (93.8%)	962 (94.5%)	-0.7 (-3.5, 2.2)	0.65
Participants with one or more adverse events, n (%)				
Total – Any grade 1–4	306 (31.9%)	125 (13.0%)	18.9% (14.2 ; 23.6)	< 0.000
Grade 1 or 2 adverse event	290 (30.2%)	111 (11.5%)	18.7% (14.0 ; 23.3)	< 0.000
Grade 3 or 4 adverse event	29 (3.0%)	19 (2.0%)	1.0% (-0.3 ; 2.4)	0.140
No adverse events	354 (68.1%)	837 (87.0%)	-18.9% (-23.6 ; 14.2)	< 0.000

Secondary safety outcome shown in the shaded row, grade 3–4 adverse events were graded by a blinded expert clinical panel.

Table A5.8. Deaths occurring during and after the treatment period

Variable	Levofloxacin (N=1023)	Placebo (N=1018)	Risk difference (5% CI)	*P value*
Total study population	1023	1018		
Total deaths	4 (0.4%)	3 (0.3%)	0.1 (-0.4 ; 0.6)	0.71
Deaths during treatment period	0 (0%)	0 (0%)		
Deaths occurring after treatment	4 (0.4%)	3 (0.3%)	0.1 (-0.4 ; 0.6)	0.71
Cause of death: TB related	0 (0%)	0 (0%)	Not estimated	Not estimated
Cause of death: Cancer	2 (0.2%)	0 (0%)	Not estimated	Not estimated
Cause of death: Stroke	0 (0%)	2 (0.2%)	Not estimated	Not estimated
Cause of death: Uncertain	2 (0.2%)	1 (0.1%)	Not estimated	Not estimated

Cause of death assigned at verbal autopsy conducted at completion of the study follow-up period

Table A5.9. TPT completion

Variable	Levofloxacin n (%)	Placebo n (%)	Risk difference (%) (Levofloxacin vs placebo)	*P value*
Total	N = 1023	N = 1018		
Treatment completed	700 (68.4%)	844 (82.9%)	-14.5% (-19.4 ; -9.6)	< 0.001
Treatment not completed for any reason	323 (31.6%)	174 (17.1 %)		
Death during treatment, not related to therapy	0 (0%)	0 (0%)	0 (0)	Not applicable
Diagnosis of active TB during treatment	0 (0%)	4 (0.4%)	-0.4%	Not applicable
Never started therapy, participant's decision	63 (6.2%)	56 (5.5%)	0.7% (-2.2 ; 3.5)	0.65
Took at least 80% of treatment (144 doses) in > 270 days	16 (1.6%)	17 (1.7%)	-0.1% (-1.3 ; 1.1)	0.858
Stopped due to participant's decision, but not a medical decision	237 (23.2%)	93 (9.1%)	14.0% (10.1 ; 17.9)	< 0.0001
Stopped due to a medical decision	7 (0.7%)	4 (0.4%)	0.3 (-0.3 ; 0.9)	0.365
Therapy stopped permanently due to adverse events[a]				
Any adverse event	71 (6.9%)	11 (1.1%)	6.0% (4.0 ; 7.7)	< 0.0001
Grade 1 or 2 adverse event	61 (6.0%)	7 (0.7%)	5.3 % (3.5 ; 7.0)	< 0.0001
Grade 3 or 4 adverse event	12 (1.2%)	4 (0.4%)	0.8% (-0.2 ; 1.5)	0.043
Death	0 (0%)	0 (0%)	0 (0%)	-

[a] One participant stopped due to both a grade 3–4 and grade 1–2 adverse events.

Overall trial conclusions

TB CHAMP

- Evidence of Lfx efficacy with substantial effect size: 1.1% in Lfx arm vs 2.6% in placebo arm (HR, 0.44 [95% CI 0.15 ; 1.25])
- Stronger evidence of treatment effect in site-assessed end-points and Bayesian analysis
- Lfx extremely safe in children: only 6 children in Lfx arm discontinued treatment early due to AEs compared, with 1 in the placebo arm
- Rate TB end-points lower than expected
- A high proportion of children were screened out with presumptive TB
- Lower IGRA positivity than expected. Power calculation assumed 40%+ vs 20%.

V-QUIN

- Lfx associated with a 45% reduction in microbiologically confirmed incident TB at 30 months.
- Few event resulted in broad confidence limits in the primary analysis, which spanned the null (not statistically significant)
- The incidence of grade 3–4 AEs was low, and no difference was seen between groups
- No acquired drug resistance to Lfx was observed
- About three times as many co-prevalent as incident TB cases
- In a sub-study, microbiome diversity was persistently reduced 6 months after therapy, with an increase in nasal carriage of FQ-resistant *Staphylococcus aureus*, a type associated with greater virulence

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

Harsimren Sidhu, Siobhan Carroll, Dick Menzies[9]

Introduction

Two randomized trials (V-QUIN and TB CHAMP) investigating safety, efficacy and tolerability of 6-month daily Lfx (6Lfx) treatment as TPT for individuals exposed to multidrug-/rifampicin-resistant tuberculosis (MDR/RR-TB) were completed in 2023. The aim of this review was to systematically review other published data from trials or observational studies on the efficacy, safety and tolerability, completion, acceptability, resource requirement, feasibility of implementation, cost-effectiveness and impact on equity of FQ regimens for TPT among all MDR/RR-TB contacts, to inform the Guideline Development Group tasked to revise the WHO TPT guidelines in December 2023. This review updated one conducted in 2016 to inform the 2018 WHO TPT guideline. The scope included studies of the efficacy and safety of other TPT regimens for MDR/RR-TB.

Methods

Research questions

1. What are the efficacy, safety, tolerability, acceptability, resource requirement, feasibility, cost-effectiveness and impact on equity of Lfx (or moxifloxacin (MFX) given as TPT in people of all ages and settings exposed to MDR/RR-TB?
2. What are the safety and efficacy of all other TPT drug regimens for individuals in contact with MDR/RR-TB patients?

For both objectives, searches were performed in PubMed, Embase, Turning Research Into Practice (TRIP) and the Global Health Library. For randomized trials, the Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. No language restriction was set for any of the searches. Relevant studies were also identified in the reference lists of relevant studies.

Inclusion criteria

Objective 1:

- Use of FQ (Lfx/MFX) TPT for contacts of MDR/RR-TB index patients.
- At least one of the following outcomes reported: TB disease incidence, change in TB-related and all-cause mortality, adverse events, treatment completion rate, emergence of additional FQ resistance in TB strains or in the microbiome other than TB strains, resources required for implementation, impact on equity, patient and health-care worker values and acceptability of FQ-based TPT, cost-effectiveness and feasibility.
- Study designs: any longitudinal design (cohorts, case–control studies, case series, population-based observational studies), cost-effectiveness modelling and RCTs.

Objective 2:

- Must include one of the following TPT regimens: 6 or 9H, 12H, 18–36H, 3 or 4HR, 1HP, 3HP, 4R, bedaquiline, delamanid, ethambutol (EMB), ethionamide/ protionamide (ETH/PTH) or other recommended TPT regimens (not Lfx or MFX).

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- Must include one of the following outcomes: TB disease incidence, prevention of disease, estimated TB-related and all-cause mortality and risk of adverse events.
- Study design: randomized control or observational studies.

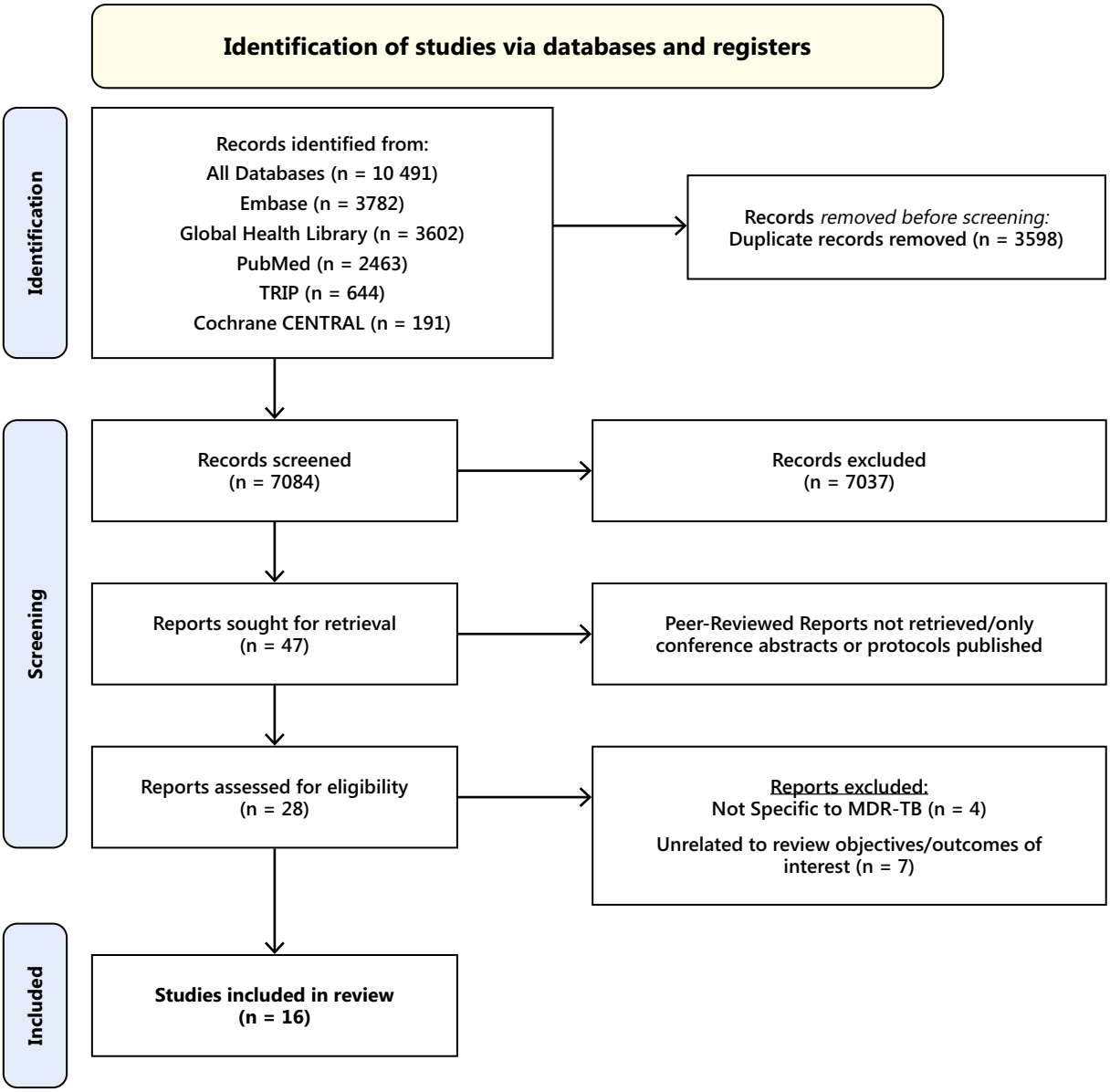
Exclusion criteria

Literature reviews, abstracts, case reports, opinion articles, grey literature. For objective 2 specifically, studies that did not provide denominators to allow estimates of TB disease incidence or incidence (risk) of adverse events or had fewer than 20 participants.

Quality assessment of included studies

Two reviewers independently evaluated the design and the quality of the evidence in the included articles. Differences were resolved through discussion until a consensus was reached. For observational studies, a quality assessment questionnaire was developed to evaluate bias with items from the Newcastle–Ottawa Scale *(1)*. The cross-sectional studies (with acceptability as the outcome) were evaluated using the AXIS tool and the one cost-effectiveness study included was evaluated using the Joanna-Briggs Institute critical appraisal tool for economic evaluations *(2,3)*. All studies were categorized into either "high", "medium", or "low" risk of bias for all items on the quality assessment forms. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework was used to evaluate the quality of study evidence.

Fig. A5.3. PRISMA flow diagram of screening



No RCTs were found. All the studies included were observational, and no studies of resource requirements, feasibility or impact on equity were found. Four of the 16 studies included efficacy: one with MFX or ofloxacin (OFX) monotherapy, two with Lfx or MFX with a companion drug (ETH, EMB or PZA and one with standard INH therapy. Five studies reported on safety outcomes, four of which were of children and adolescents and one of adult contacts. Six studies reported the acceptability of FQ-based TPT; five reported quantitative measures and one the qualitative acceptability of a novel paediatric Lfx formulation to caregivers and child contacts. One study evaluated the global cost-effectiveness of providing Lfx to HHCs < 15 years. The studies included were too disparate to allow any pooling of results or meta-analyses. Therefore, the results below reflect non-pooled findings. The protocol of this systematic review was registered on Prospero on 23 September 2023 (ID: CRD42023462793).

Results and quality of evidence

Efficacy of TPT regimens for contacts exposed to MDR-TB

Table A5.10. Observational studies evaluating the efficacy of FQ-based TPT regimens to prevent TB among HHCs of MDR-TB patients

Reference	Setting	Population	Intervention(s)	Control(s)	Outcome definition	Proportion of participants who developed TB disease
Studies of TPT including child and adolescent HHCs of patients with MDR-TB						
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Household contacts aged < 18 years (n=72)	9MFX (n=55)[a]	Child contacts with caregivers who refused TPT (n=14)	People with culture-confirmed TB within 2 years of follow-up	MFX: 0/55 Refused TPT: 1/14
Malik et al. (2021) *(5)*	Karachi, Pakistan	Household contacts of all ages (n=799)	6-month FQ (Lfx/MFX) + ETH/EMB (n=172)	Refused TPT (n=43) Considered ineligible for TPT (n=574)	People with culture-confirmed TB within 2 years of follow-up	Any TPT: 2/172 Refused TPT: 0/43 Ineligible: 0/574
Studies of TPT among close adult contacts of MDR-TB						
Bedini et al. (2016) *(6)*	Penitentiary in Modena, northern Italy	Incarcerated adults in close contact with MDR-TB (n=17)	6-month Lfx + PZA (n=12)	Refused TPT (n=5)	People with incident TB disease during 24 months of follow-up	Lfx + PZA: 0/12 Refused TPT: 0/5

9MFX, 9 months of moxifloxacin; FQ, fluoroquinolone; Lfx; levofloxacin; MDR-TB, multidrug-resistant TB; ETH, ethionamide; EMB, ethambutol; PZA, pyrazinamide.

[a] Three participants were treated for 9 months with ofloxacin but are not cited here due to stronger evidence from other studies with different estimates of efficacy.

Overall, the studies show that FQ-based TPT is not associated with a significant reduction of TB disease. Quality assessment suggests considerable risk of selection bias and small sample sizes, making estimates of efficacy imprecise. Gureva et al. *(4)* used a very small comparator group and was biased, as refusal was likely to be associated with other factors that affect health outcomes. INH was found to be effective for MDR-TB contacts in the study by Huang et al. *(7)* (incident TB aHR 0.19) conducted among children and adolescents < 19 years in Lima, Peru (see Table A5.11); however, potential selection bias in this study was high. The reason why the comparator group was untreated with INH is unclear but was presumably due to refusal. The mean duration of INH treatment was 115 days due to cessation TPT when multidrug resistance was confirmed, which is significantly shorter than the usual 180 days.

Table A5.11. Summary of a prospective cohort study evaluating of the efficacy of INH TPT for HHCs of MDR-TB index patients *(7)*

Reference	Setting	Population	Intervention	Control	Type of outcome	People who developed TB disease / person-years of follow-up
Huang et al. (2020) *(7)*	Lima, Peru	Children/ adolescents aged ≤ 19 who were HHCs of MDR-TB index patients (n=666)	INH[a] (n=265)	No INH (n=401)	Culture-confirmed TB disease per person-year (≥ 1 year of follow-up)	**Overall** INH: 3/320 No INH: 23/474 aHR[b], 0.19 [95% CI, 0.05 ; 0.66] Child contacts (< 5 years) INH: 2/144 No INH: 10/145 HR, 0.19 [95% CI, 0.04 ; 0.98]

HHCs, household contacts; aHR, adjusted hazard ratio; INH, isoniazid

[a] Duration of treatment varied among participants, as some were told by their physicians to stop treatment after MDR-TB confirmation.

[b] Hazard ratio adjusted for index case age, recreational drug use, HHC, age, sex, bacillus Calmette-Guérin vaccination scar, nutritional status, being a student, TB history, household socioeconomic status and household residential district.

Safety of TPT regimens used among MDR-TB contacts

Table A5.12. Summary of studies evaluating the safety of FQ-based TPT regimens for children and adolescent (< 18)

Reference	Setting	Population	Intervention(s) or exposure(s)	Outcome(s) reported	Outcome estimate
Apolisi et al. (2023) *(8)*	Khayelitsha, Cape Town, South Africa	Children and adolescents aged 0–18 years who were s HHC of an MDR-TB index case (n=95)	6Lfx (n=79) or 6INH (n=9)	Mild or moderate AE reported during TPT Serious AE Treatment discontinuation due to drug-related AE	6Lfx: 8/79 6INH: 0/9 None 6Lfx: 3/79 6INH: 0/9
Garcia-Prats et al. (2019) *(9)*	Cape Town, South Africa	Children < 5 years who were HHC of an MDR-TB index case (n=27)	Short-term pharmacokinetics provision of novel 100 mg paediatric Lfx dispersible tablets	Grade 1 or 2 AE at least possibly related to Lfx Grade 3 or 4 AE at least possibly related to Lfx Lfx discontinuation due to drug-related AE	2/27 0/27 0/27
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Children aged < 18 years who were HHC of an MDR-TB index case (n=72)	9MFX (n=55) or 9OFX (n=3)	Grade 1 or 2 drug-related AE Treatment discontinuation due to drug-related AE Proportion completing TPT	6/58 1/58 52/58 (90%)
Malik et al. (2020;2021) *(10,11)*	Karachi, Pakistan	HHC of all ages exposed to MDR-TB index case (n=172)	6-month ETH + FQ (Lfx or MFX) (n=59) 6-month EMB + FQ (Lfx or MFX) (n=113)	Grade 1 or 2 drug-related AE Children < 5 years who reported AE Treatment discontinuation due to drug-related AE Proportion completing TPT	ETH + FQ: 20/59 EMB + FQ: 16/113 6/61 11/172 (6%) 121/172 (70%)

6Lfx, 6-months of levofloxacin; 6INH, 6 months of isoniazid; 9MFX, 9 months of moxifloxacin; 9OFX, 9 months of ofloxacin; HHC, household contacts

Of the five studies evaluating the safety of FQ-based TPT among exposed MDR-TB contacts, three reported AE and treatment discontinuation after FQ monotherapy with either Lfx, OFX or MFX alone (Table A5.12). No serious or grade 3/4 AE were reported in these studies and very low discontinuation of FQ treatment. The AE rates were higher in the study of Malik et al. *(10)*, in which Lfx/MFX was given with ETH or EMB, and in the study by Bedini et al. *(6)* in which contacts received Lfx and PZA (Table A5.13). Malik et al. found a higher proportion of grade 1 or 2 AE with ETH than with EMB, and 11 of the 36 contacts discontinued TPT. Similarly, in the study by Bedini et al. *(6)*, the combination of Lfx and pyrazinamide was poorly tolerated.

Table A5.13. Summary of study evaluating the safety of FQ-based TPT regimens among adult HHCs of MDR-TB index patients

Reference	Setting	Population	Intervention/ exposure	Outcomes reported	Outcome estimates
Bedini et al. (2016) *(6)*	Penitentiary in Modena, northern Italy	Incarcerated adults in close contact with MDR-TB case (n=17)	6-month Lfx + PZA (n=12)	Any AE Treatment discontinuation due to drug-related AE Completed 6-month TPT regimen	9/12 7/12 (58%) 5/12 (42%)

AE, adverse events; Lfx, Levofloxacin; MDR-TB, multidrug-resistant TB; PZA, Pyrazinamide; TPT, TB preventive treatment

The objective of the review was to determine the safety of FQ in MDR prevention or treatment. Data from three studies that reported AEs attributable to Lfx or MFX were retrieved. A study by Ali et al. *(12)* addressed acute Fridericia-corrected QT interval (QTcF) responses to experimentally administered TB drugs, including Lfx and MFX, either alone or in combination with another drug. MFX given alone resulted in only one mild (grade 1) QTcF prolongation in 32 patients, and Lfx alone resulted in QTcF prolongation in 19 patients. A pharmacokinetics study by Jin et al. *(13)* reported a significant association between higher Lfx concentration and increased QTc intervals; however, the QTc intervals decreased over time, and there was no significant difference from pre-treatment intervals by the end of 12 months. Treatment was not discontinued in any patient, and no patients experienced cardiac adverse events. A study conducted by Garcia-Prats et al. *(14)* among 70 children aged < 15 years treated for MDR-TB disease found a significant number of grade 1 AE (59/70) and grade 2 AE (11/70) that were related to Lfx. Only one child experienced a grade 3 AE, and no children experienced grade 4 AE. Treatment was not discontinued.

Acceptance, willingness and acceptability of FQ-based TPT regimens

For this review, two quantitative and one qualitative outcome were considered for acceptance (actually starting), stated willingness to start (theoretical) and acceptability according to on qualitative methods. Acceptance was defined as the proportion of eligible contacts who accepted and started TPT when offered.

Table A5.14. Summary of studies of acceptance to start FQ-based TPT among caregivers and MDR-TB HHCs

Reference	Setting	Population	Intervention	Outcome definition	Acceptability: agreed to start
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Children < 18 years who were HHCs of an MDR-TB index case (n=72)	9-month FQ (MFX or OFX)	Proportion of caregivers who agreed for a child to start TPT with OFX/MFX	58/72 (81%)
Malik et al. (2021) *(5)*	Karachi, Pakistan	Household contacts of all ages exposed to an MDR-TB index case (n=215)	6-month FQ (Lfx or MFX) + ETH or EMB	TPT-eligible participants who accepted to start treatment	172/215 (80%)

ETH, ethionamide; EMB, ethambutol; FQ, fluoroquinolone; HHC, household contacts; Lfx, levofloxacin; MFX, moxifloxacin; OFX, ofloxacin; TPT, TB preventive treatment

The reported degree of acceptance in these two studies was relatively high (Table A5.14). Gureva et al. *(4)* reported acceptance of 81% with MFX or OFX and Malik et al. found 80% acceptance of Lfx or MFX and a companion drug (ETH or EMB). Strong willingness was noted among adult and adolescents (Table A5.15), which, however, dropped for TPT that had potential side-effects.

Table A5.15. Studies of willingness to start hypothetical fluoroquinolone-based TPT among caregivers and MDR-TB HHCs

Reference	Setting	Population	Outcome definition	Acceptability: willingness to start
Rouzier et al. (2022) *(15)*	Botswana (1 site), Brazil (1), Haiti (1), India (2), Kenya (1), Peru (2), South Africa (7), Thailand (1)	Adult and adolescent HHC who reported caring for children < 13 years of age (n=299)	Proportion of caregivers willing to administer daily TPT pill to their children have their children complete prerequisite steps to determine MDR TPT eligibility	278/299 (93%) 283/299 (95%)
Suryavanshi et al. (2019) *(16)*	Same as above	Adolescent and adult HHC of MDR-TB index cases (n=743)	Percentage of HHC willing to take a hypothetical, newly developed TPT take TPT with potential mild, temporary side-effects	79% 70%

HHC, household contacts; MDR-TB, multidrug-resistant TB; TPT, TB preventive treatment

The acceptability of Lfx, i.e. willingness and ability to adhere to a TPT regimen, was addressed in two studies of a novel child-friendly Lfx formulation. Purchase et al. *(17)* found high acceptability among children and their caregivers; for example, 81% of caregivers found the formulation easier to prepare than the adult formulation, and 82% found the size of the tablet to be acceptable. Wademen et al. *(18)* also found high acceptability, although caregivers expressed concern about the financial and care burden, especially when they themselves were on treatment for MDR-TB disease.

Cost-effectiveness of TPT among children exposed to MDR-TB

The cost-effectiveness of several contact management strategies was examined by modelling in a study by Dodd et al. *(19)* (Table A5.16). The authors reported that provision of TPT with screening and treatment of co-prevalent TB disease was more cost-effective than detection and treatment of disease among HHCs of MDR-TB patients alone. TPT for groups at highest risk was the most cost-effective strategy, and providing TPT to all children under 15 averted most deaths and the greatest reduction in life-years lost. When the analysis was updated with efficacy estimates from the TB CHAMP and V-QUIN trials, the results were similar (unpublished data provided by J. Seddon).

Table A5.16. Summary of Dodd et al. *(19)* global modelling study on the cost-effectiveness of several MDR-TB HHC management scenarios for children < 15 years

Household contact management scenario	Life-years lost, 3% discounted (thousands)	Total deaths averted	Deaths averted with TPT provision	ICER (US$ per DALY)
No detection or treatment of co-prevalent TB disease; no TPT (baseline scenario)	171	–	–	–
Detection and treatment of co-prevalent TB disease for HHCs aged < 15; no TPT	105	2350	–	960
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 5 and children < 15 with HIV	80.6	3220	870	738
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 5 years and children < 15 with HIV or TST-positive	72.6	3510	1160	773
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 15	70.3	3590	1240	838

6Lfx, 6 months of levofloxacin; 6MFX, 6 months of moxifloxacin; HHC, household contacts; ICER, incremental cost-effectiveness ratio; DALY, disability-adjusted life year; TPT, TB preventive treatment; TST, tuberculin skin test

Conclusion

No randomized controlled trials that addressed the objectives of this systematic review were identified. Hence, no high-quality evidence on the efficacy of FQ-based TPT for MDR-TB contacts was found. All the observational studies identified had problems of selection bias and small samples; none suggested any significant benefit of use of FQ-based TPT to prevent development of MDR-TB disease. Although the quality of evidence was low, the results from larger observational studies suggest that FQ-based TPT is safe for use among MDR-TB contacts. No grade 3, 4 or serious adverse events related to Lfx or MFX were reported, and FQ monotherapy had high completion rates and acceptability. Mild or moderate adverse events were observed in children and adolescents. A high-quality modelling study evaluating cost-effectiveness found that targeting the highest risk groups – children < 5 or < 15 years with HIV – was the most cost-effective, but provision of FQ TPT to all contacts < 15 years would have greater impact and still be more cost-effective than detection of prevalent TB disease alone. Higher quality evidence is necessary on the efficacy of FQ-based TPT for prevention of MDR-TB disease among contacts.

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A5.3 Assessing fluoroquinolone (levofloxacin) acceptability among contacts of MDR-TB patients: a qualitative study[10]

Objective: to assess the values, preferences, acceptability and feasibility of Lfx as TPT for adult HHCs of patients diagnosed with MDR-TB in five low- and middle-income countries: Georgia, India, Indonesia, South Africa and Viet Nam.

Sampling and recruitment strategy: Eligible participants who were contacts of newly diagnosed MDR-TB patients were identified in the five countries. In South Africa and Viet Nam , collaborators also recruited participants who were part of the V-QUIN and TB CHAMP trials, including participants who did and did not complete the study treatment due to adverse events. Collaborators at each site explained the project briefly to potential participants. Interviews were conducted in the presence of a skilled interpreter where required. Informed consent, written or verbal, was obtained before the interview.

Eligibility criteria

Inclusion:

- household contact of a person diagnosed with MDR-TB.
- eligible for TPT according to WHO guidelines *(1)*.

Exclusion:

- < 18 years
- unable to provide informed consent
- unable to be interviewed in Cantonese, English, French, Mandarin or Punjabi or interpreter not available.

Methods

A trained qualitative researcher conducted one-on-one interviews with a semi-structured interview guide with the participants over telephone or online. Trained interpreters, hired by the interviewers, were present when required. The interviews lasted 30–60 min. The interviewer asked participants about their attitude, values and perspectives towards use of FQs as TPT and sought to understand the risk–benefit considerations underlying their decisions. Participants were informed of the estimates of effectiveness and side-effects from the preliminary results of the randomized trial study populations in Viet Nam (adults) and South Africa (children). They were also informed about the risks of MDR-TB disease, and the difference from TB infection, and risks and burden of MDR-TB treatment, including treatment duration, adverse events and treatment outcomes. This allowed participants to make an informed decision on whether they preferred TPT to an increased risk of developing MDR-TB disease. Interviewers at each site recorded demographic and clinical information, including age, sex, level of education, comorbidities and TB history on a patient enrolment form. Data were analysed with an inductive approach. Thematic analysis was used to identify and highlight recurring themes.

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Table A5.17. Study participants (n=36)

Characteristic	n	% or range
Country		
Georgia	7	19
India	10	28
Indonesia	5	14
South Africa	9	25
Viet Nam	5	14
Female	19	53
Median age (years)	41	21–67
Employed	22	61
Chronic condition[a]	11	31
Offered TPT[b]	9	25
Accepted	6	17

[a] Diabetes, cardiovascular disease, chronic gastritis, joint pain/arthritis, HIV

[b] 2/2 were offered and accepted TPT for DS-TB, 4/7 were offered and accepted TPT for MDR-TB (6-month Lfx).

Results

A total of 36 participants were interviewed (Table A5.17).

Acceptability of TPT for MDR-TB involved a decision on whether:

- TPT held value for them ("values");
- TPT effectiveness, requirements and safety met their subjective thresholds ("preferences"); and
- they anticipated being able to complete the treatment successfully ("feasibility").

The participants' values were influenced by their sociocultural and economic contexts, as well personal and community experiences with MDR-TB. The values aligned with higher TPT acceptability included:

- belief in the importance of disease prevention, such as vaccination;
- general trust in medicines and doctors, "The doctor knows best, so whatever they give, I have to take." (India, 45-year-old woman);
- fear of MDR-TB disease, its treatment and contagiousness, "I would feel so bad if I got MDR-TB, it will be very painful….TPT is a good thing because I have younger grandkids and we don't know when they will catch it." (South Africa, 50-year-old woman).
- A participant's values could override the perceived benefits and harms of TPT. For instance, a few participants who did not value disease prevention would refuse MDR TPT, regardless of its potential effectiveness, low requirements and safety, unless it was mandatory.

Among participants who found value in TPT, acceptance depended on their subjective thresholds for treatment effectiveness, dosage and schedule and adverse drug reactions. For instance, participants would tolerate mild-to-moderate side-effects and long treatment duration, if they had a minimum level of efficacy (such as reducing the risk of disease by 50%), but not if TPT efficacy was below that threshold. Given an acceptable level of efficacy, most participants prioritized safety over treatment duration; treatment schedule was considered the least important. The final consideration of acceptability was perceived feasibility. Participants who valued TPT reflected on demands on their lives due to TPT. They considered the following as potential barriers: out-of-pocket expenses (e.g. transport); disruption due to clinical follow-up, time commitment and requirement for child-care arrangements; lack of social and financial support; and insufficient treatment counselling and education.

Overall, MDR TPT was acceptable and held a high social value among participants in the five settings. The most acceptable regimen would have high effectiveness in preventing MDR-TB, mild toxicity, little interference with daily activities, low pill-burden, minimal and convenient clinical follow-ups, and low cost to the participants.

Reference

1. WHO operational handbook on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240002906).

A5.4 A survey to explore the programmatic feasibility of levofloxacin (Lfx) TPT for MDR-TB contacts[11]

Introduction

The survey assessed the feasibility of programmatic use of Lfx for TPT among contacts of MDR-TB patients in the eventuality of a WHO recommendation for its programmatic use. The objective was to collect perspectives from national TB programmes (NTPs), explore current practices for MDR TPT, its programmatic feasibility, affordability, impact on equity, acceptability to patients and health-care workers and to inform the discussion of WHO Guideline group at its meeting on 4–6 December 2023.

Methods

Sampling and recruitment strategy: Purposive sampling of NTP managers in 30 countries listed by the WHO as having the highest burden of MDR-TB who were contacted from publicly listed e-mail addresses. 18 programme managers responded within the expected timeline, comprising three in the WHO African Region, two in the South-East Asia Region, seven in the European Region, one in the Eastern Mediterranean Region, and five in the Western Pacific Region. The perspectives of NTP managers were collected on a self-administered, short-answer survey questionnaire sent by e-mail.

Results

Current practice in use of MDR TPT among contacts of DR/MDR-TB patients: Seven (39%) of 18 NTP managers reported use of 6Lfx for MDR-TB contacts, although in two countries use was limited due to high background resistance to FQs. One respondent each reported use of 9-month Lfx as a part of a two-drug regimen with either ethionamide or prothionamide as a companion drug, high-dose INH and either 6-month standard dose INH or 3 months of once-weekly INH and rifapentine. Three (17%) did not specify the TPT regimen being used. Eight (44%) respondents reported no use of TPT for contacts of DR/MDR-TB patients.

Affordability: Respondents were informed about the estimated cost of providing 6Lfx at the Global Drug Facility price per treatment course (approximately US$ 18.50, as compared with 6H at US$ 3.50 and 9H at US$ 5.25). Most respondents considered 6Lfx to be affordable. Nine (50%) stated that it would be affordable for all ages, three (17%) that it would be affordable only for HHCs < 15 years and one (6%) only for HHCs < 5 years. Three (17%) respondents stated that 6Lfx would not be affordable and two (11%) that it would depend on the availability of donor funding.

Programmatic feasibility (additional resources required, distribution, training, timeline): Nine (50%) of the 18 respondents suggested that the cost and the availability of additional resources would not be barriers to implementation, while seven (39%) considered that additional funding would be necessary for expansion of drug-susceptibility testing, contact screening, monitoring and follow-up for individuals started on TPT. Five (28%) respondents noted that implementation of 6Lfx TPT would divert resources from other services and called for proactive planning. All the managers stated that logistics management for Lfx would be sustainable. Nine (50%) managers stated that no training or < 12 h of additional training would be required for health-care workers, and four (22%) respondents said that > 12 h of training would be necessary.

With regards to the timeline for nationwide scaling up of 6Lfx TPT, nine (50%) respondents estimated that it would take <3 years and one (6%) stated >3 years. The others either did not provide information or were unsure. Acceptability to health-care workers was generally anticipated to be high, five (28%) respondents expected health-care workers to remain neutral, some expressed concern about fear

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of Lfx resistance by health-care workers and that TPT uptake remains low among contacts of drug-susceptible TB patients. Acceptability among recipients was also anticipated to be relatively high given the severity of MDR-TB disease, stigmatization and resulting socioeconomic challenges. Other challenges may include lack of community awareness, long duration of TPT and potential side-effects.

Equity considerations: NTP managers expected equity to be increased due to prevention of MDR-TB disease, although six (33%) respondents expressed concern about access in remote locations, and two mentioned a risk of drug shortages if computation of requirements is based on notification data. Eleven (61%) respondents also raised concern about increased out-of-pocket spending for contacts, and two (11%) mentioned that health insurance does not cover TB treatment.

Implementation decisions: Seven respondents reported current use of 6Lfx, and eight expressed willingness to implement it immediately or after a few years provided WHO made a strong recommendation. Only two (11%) respondents stated that they would not implement 6Lfx despite a strong recommendation. In the case of a conditional WHO recommendation, seven (39%) respondents stated that programmatic implementation was less likely, while some mentioned slow or staggered implementation or faster introduction in some regions than in others.

Conclusion

Most national programme managers were willing to use 6Lfx for MDR-TB contacts after a strong WHO recommendation. 6Lfx is anticipated to be generally affordable and feasible, would increase equity and would be acceptable to both health-care workers and contacts. Specific concerns of national programme managers were constraints in funding, human and other resources, fear of increased Lfx resistance and increased out-of-pocket spending, which would reduce equity. Although not all countries responded, those that did can be considered reasonably representative. As this was a short cross-sectional, self-administered survey, broader programmatic perspectives of NTP managers about the affordability or feasibility of obtaining additional resources could not be evaluated.

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