

Latent tuberculosis infection

Updated and consolidated guidelines for programmatic management

ANNEX 2

Evidence-to-Decision and GRADE tables

Latent tuberculosis infection

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Annex 2. Evidence-to-Decision and GRADE tables



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PICO1: What is the prevalence of LTBI, risk of progression to active TB and cumulative prevalence of active TB among household contacts without HIV in different age groups in high TB incidence countries?

Problem	Identification of household contacts for diagnosis and treatment of LTBI	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.
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	

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 TB preventive treatment is given. Although WHO currently recommends systematic LTBI screening and treatment for household contacts of any age in low-TB incidence countries, it is recommended only for child household contacts < 5 years old in high-TB incidence countries.	
Balance of effects	Do the benefits outweigh the harms? <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> They are equal <input type="radio"/> 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 the 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.	

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 \geq 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)
\geq 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

Age (years)	Baseline LTBI status positive		Regardless of baseline LTBI status	
	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)
\geq 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 have lower risk of the development of active TB compared to children < 5 years. Furthermore, in the second and the third review, we compared the risk of active TB among household contacts stratified by age groups compared to the general population using year- adjusted national estimated TB incidence from the WHO.

Balance of effects		<p>Pooled estimates of risk of development of active TB among household contacts stratified by age and baseline LTBI status compared to the general population.</p> <table border="1"> <thead> <tr> <th rowspan="3">Age (years)</th> <th rowspan="3">No. of studies (no. of participants)</th> <th colspan="4">Baseline LTBI status positive</th> <th colspan="4">Regardless of baseline LTBI status</th> </tr> <tr> <th colspan="2">Follow-up <12 months</th> <th colspan="2">Follow-up <24 months</th> <th colspan="2">Follow-up <12 months</th> <th colspan="2">Follow-up <24 months</th> </tr> <tr> <th>Risk ratio</th> <th>#studies (no. of participants)</th> <th>Risk ratio</th> <th>#studies (no. of participants)</th> <th>Risk ratio</th> <th>#studies (no. of participants)</th> <th>Risk ratio</th> <th>#studies (no. of participants)</th> </tr> </thead> <tbody> <tr> <td>General population</td> <td>-</td> <td>1.0 (Reference)</td> <td>-</td> <td>1.0 (Reference)</td> <td>-</td> <td>1.0 (Reference)</td> <td>-</td> <td>1.0 (Reference)</td> </tr> <tr> <td>0-4</td> <td>2 (265)</td> <td>24.32 (0.73-811.02)</td> <td>3 (585)</td> <td>22.87 (7.65-68.63)</td> <td>3 (1930)</td> <td>25.86 (16.87-39.66)</td> <td>5 (2773)</td> <td>14.8 (9.82-22.3)</td> </tr> <tr> <td>5-9</td> <td>1 (298)</td> <td>30.98 (14.26-67.31)</td> <td>1 (298)</td> <td>15.49 (7.89-30.4)</td> <td>1 (1464)</td> <td>18.39 (9.75-34.68)</td> <td>1 (1464)</td> <td>9.2 (5.55-15.23)</td> </tr> <tr> <td>10-14</td> <td>1 (363)</td> <td>55.1 (28.55-106.33)</td> <td>1 (363)</td> <td>27.55 (16.16-46.96)</td> <td>1 (1340)</td> <td>25.83 (13.97-47.76)</td> <td>1 (1340)</td> <td>12.92 (8.0-20.86)</td> </tr> <tr> <td>5-14</td> <td>2 (728)</td> <td>27.13 (17.47-54.07)</td> <td>3 (1203)</td> <td>8.22 (2.3-29.36)</td> <td>3 (3067)</td> <td>24.11 (16.89-34.43)</td> <td>5 (4197)</td> <td>6.29 (2.88-13.72)</td> </tr> <tr> <td>≥15</td> <td>1 (3879)</td> <td>30.74 (17.46-54.07)</td> <td>2 (4450)</td> <td>13.35 (9.46-18.83)</td> <td>1 (9380)</td> <td>24.68 (14.18-42.98)</td> <td>3 (10531)</td> <td>11.67 (7.55-18.02)</td> </tr> </tbody> </table> <p>The results showed that household contacts have substantially higher risk of active TB compared to the general population regardless of their age.</p>	Age (years)	No. of studies (no. of participants)	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		Risk ratio	#studies (no. of participants)	Risk ratio	#studies (no. of participants)	Risk ratio	#studies (no. of participants)	Risk ratio	#studies (no. of participants)	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 (1930)	25.86 (16.87-39.66)	5 (2773)	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 (1464)	18.39 (9.75-34.68)	1 (1464)	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 (1340)	25.83 (13.97-47.76)	1 (1340)	12.92 (8.0-20.86)	5-14	2 (728)	27.13 (17.47-54.07)	3 (1203)	8.22 (2.3-29.36)	3 (3067)	24.11 (16.89-34.43)	5 (4197)	6.29 (2.88-13.72)	≥15	1 (3879)	30.74 (17.46-54.07)	2 (4450)	13.35 (9.46-18.83)	1 (9380)	24.68 (14.18-42.98)	3 (10531)	11.67 (7.55-18.02)	
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Certainty of evidence	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 																																																																																		
Values	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> No important uncertainty or variability <input checked="" type="radio"/> Minimal uncertainty 	<p>We conducted an online survey (Annex 3) to solicit the values and preferences of individuals affected by the recommendations. Responses were available from 142 respondents with a median age of 46 years (IQR: 37-54 years). More than 80% of the respondents reported that they would strongly or somewhat prefer to receive TB preventive treatment 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.</p>	<p>Concern about whether the respondents in the online survey correctly reflect the values of clients.</p>																																																																																

Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Greater resource requirements with the intervention <input type="radio"/> Less resource requirements with the intervention <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>National programmes could build upon existing programmes for children < 5 years, which could reduce the additional resource requirements.</p>
Cost effectiveness	<p>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input type="radio"/> Favours the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 	<p>A systematic review of the cost-effectiveness of management of LTBI was undertaken for the 2015 WHO LTBI guidelines. The review covered six studies on 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.</p>	<p>Cost-effectiveness data from low-TB incidence countries may not be applicable to high-TB incidence countries, where the risk for re-infection is high. However, the GDG noted data suggesting the durability of protection in high-TB incidence countries.</p> <p>A recent modelling study suggested that preventive treatment without LTBI testing is cost-effective for child contacts < 5 years old (1).</p>
Equity	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 		

Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>		<p>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.</p>
Feasibility	<p>Is the intervention feasible to implement?</p> <p><input type="radio"/> No</p> <p><input type="radio"/> Yes</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>		<p>Depends on setting, health infrastructure (e.g. availability of test and drugs) and population groups (e.g. adolescents).</p>

Summary of judgements

Problem	Judgement							Implications
	No		Equal	Yes		Varies	Unknown	
Balance of effects	No		Equal	Yes			Uncertain	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability		Minimal uncertainty	No important uncertainty or variability				
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 included studies	
Equity	Reduced				Increased	Varies	Unknown	
Acceptability	No			Yes		Varies	Unknown	
Feasibility	No			Yes		Varies	Unknown	

Conclusions

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

Recommendation	In favour of <input checked="" type="checkbox"/>	Against <input type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input type="checkbox"/>	Conditional <input checked="" type="checkbox"/>	
Recommendation	<p>In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. (Conditional recommendation, low-quality evidence.)</p> <p><i>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.</i></p>		
Justification	<p>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.</p> <p>There was overall consensus that more resources would be required and lack of evidence on 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. However, six of the studies were conducted in low-TB incidence countries, and the GDG noted that the results are not applicable in high-TB incidence countries, where the risk for re-infection is high. The GDG also noted evidence for 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.</p> <p>There was general 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.</p>		
Subgroup considerations			
Implementation considerations	<p>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.</p> <p>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.</p> <p>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.</p>		
Monitoring and evaluation			
Research priorities	<p>Methods to improve adherence and completion rate.</p> <p>Implementation research to improve effectiveness and efficiency of managing household contacts (e.g. household-based intervention to reduce barriers).</p> <p>Development of diagnostic tests with improved performance and predictive value for reactivation of TB.</p> <p>Durability of protection by preventive treatment in TB endemic settings.</p>		

GRADE tables: SR1

SR1. Risk for LTBI 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 (2-15)	Cross-sectional	Not serious ^{1,2}	Serious ³	Not serious	Not serious ⁴	2265/8507	1298/9526	1.62 (1.25;2.11)	85.1 (34.2;151.1)	Moderate	Important
AGE GROUPS COMPARED: 10-15 YEARS VS 0-5 YEARS											
11 studies (2,4,6,8,9,10-15)	Cross-sectional	Not serious ⁵	Serious ⁶	Not serious	Not serious ⁷	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 ⁸	Cross-sectional	Serious ⁹	Serious ¹⁰	Not serious	Not serious ¹¹	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 ¹²	Cross-sectional	Not serious ¹³	Serious ¹⁴	Not serious	Not serious ¹⁵	13218/21962	1979/6763	2.04 (1.53;2.63)	293.9 (155.1;475.7)	Moderate	Important

¹ Potential selection bias in (3), as only 69% of participants were household contacts.

² Potential misclassification: Eight studies (4-6,8,11,12,14,15) 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.

³ High heterogeneity among studies ($I^2 = 94\%$), probably due to differences in background TB incidence. The risk ratios of two studies (2,6) showed opposite effects.

⁴ Small sample size in (6) ($n < 50$).

⁵ Potential misclassification: Reports of seven studies (4,6,8,11,12,14,15) 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.

⁶ High heterogeneity among studies ($I^2 = 97\%$) probably due to differences in background TB incidence. The risk ratio in one study (6) showed opposite effect.

⁷ Wide 95% CI of pooled risk ratio. Small sample size in (6) ($n < 50$) and (13) ($n < 100$).

⁸ Studies included: (4,6,9,11,13,16-26).

⁹ Potential selection bias in (17), as only 89% of participants were household contacts.

¹⁰ High heterogeneity among studies ($I^2 = 93\%$), probably due to differences in background TB incidence. The risk ratios in three studies (6,19,21) showed opposite effects.

¹¹ Small sample size in (6) and (18) ($n < 50$).

¹² Studies included: (4-6,9-11,13-16,19-27).

¹³ Potential misclassification: The reports of ten studies (4-6,11,14,15,20,21,24,27) 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.

¹⁴ High heterogeneity among studies ($I^2 = 98\%$), probably due to differences in background TB incidence.

¹⁵ Small sample size in 6 and 27 ($n < 100$).

SR2

SR2. Development of active TB disease in household contacts with LTBI 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 (9,14,17,23)	Cohort	Not serious	Not serious	Serious ¹	Not serious	Serious ²	54/1329	73/630	0.28 (0.12;0.65)	83.8 (40.3;102.3)	Low	Critical
AGE GROUPS COMPARED: > 15 YEARS VS 0-5 YEARS												
3 (9,14,23)	Cohort	Not serious	Not serious	Serious ³	Not serious	Not serious	186/4746	73/595	0.22 (0.08;0.60)	95.5 (49.1;112.6)	Moderate	Critical

Because 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.

¹ 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.

² Few events.

³ 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 active TB in household contacts, irrespective of baseline LTBI 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 (9,14,17,18, 23,28) ¹	Cohort	Not serious	Not serious	Serious ²	Not serious	Not serious	131/4389	203/2903	0.39 (0.18;0.85)	42.9 (10.6;57.6)	Moderate	Important
AGE GROUPS COMPARED: > 15 YEARS VS 0-5 YEARS												
4 (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.

¹ One outlier study (29) was excluded because of uncertainty about the cases that were included (co-prevalent vs incident cases).

² 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 active TB disease in household contacts with LTBI 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 ¹	RR (95% CI)	Absolute per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0–5 YEARS VS GENERAL POPULATION											
2 (9,17)	Cohort	Serious ²	Serious ³	Not serious	Very serious ⁴	0/35	41/10 000	24.32 (0.73;811.02)	63 (-0.7;2187.1)	Very low	Critical
						32/230	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ²	Not serious	Not serious	Serious ⁶	12/298	13/10 000	30.98 (14.26;67.31)	39 (17.2;86.2)	Low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED 10–14 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ²	Not serious	Not serious	Serious ⁶	26/363	13/10 000	55.1 (28.55; 106.33)	70.3 (35.8;136.9)	Low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED 5–15 YEARS VS GENERAL POPULATION											
2 (9,17)	Cohort	Serious ²	Not serious ⁵	Not serious	Serious ⁶	4/67	41/10 000	27.13 (17.47;54.07)	70.5 (21.3;220.7)	Low	Critical
						38/661	13/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED > 15 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ²	Not serious	Not serious	Serious ⁶	155/3879	13/10 000	30.74 (17.46;54.07)	38.7 (21.4;69)	Low	Critical

¹ LTBI does not apply to the general population.

² Ascertainment bias highly likely. 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).

³ High heterogeneity ($I^2 = 83.9\%$) among studies, probably due to differences in background TB incidence.

⁴ Serious imprecision with a wide 95% CI for the effect estimates, probably due to the small study size and number of outcome events.

⁵ $I^2 = 72.5\%$, indicating moderate heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.

⁶ Few events and wide 95% CI.

Development of active TB disease in household contacts with LTBI in high-TB incidence countries
Comparison with the general population (follow-up ≤ 24 months)¹

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 ²	RR (95% CI)	Absolute per 1000 (95% CI)		
COMPARISON: HOUSEHOLD CONTACTS AGED 0-5 YEARS VS GENERAL POPULATION											
3 (9,17,23)	Cohort	Serious ³	Serious ⁴	Not serious	Serious ⁵	0/35	82/10 000	22.87 (7.65; 68.63)	108.6 (33;334.6)	Very low	Important
						26/320	41/10 000				
						32/230	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED 5-9 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ³	Not serious	Not serious	Serious ⁵	12/298	26/10 000	15.49 (7.89;30.4)	37.7 (17.9;76.4)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10-14 YEARS VS GENERAL POPULATION											
1 (23)	Cohort	Serious ³	Not serious	Not serious	Serious ⁵	26/363	26/10 000	27.55 (16.16;46.96)	69 (39.4;119.5)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5-15 YEARS VS GENERAL POPULATION											
3 (9,17,23)	Cohort	Serious ³	Serious ⁶	Not serious	Serious ⁵	4/67	82/10 000	8.22 (2.3;29.36)	35.8 (6.5;140.8)	Very low	Important
						6/475	41/10 000				
						38/661	26/10 000				
COMPARISON: HOUSEHOLD CONTACTS AGED > 15 YEARS VS GENERAL POPULATION											
2 (9,23)	Cohort	Serious ³	Not serious ⁷	Not serious	Not serious	26/571	41/10 000	13.35 (9.46;18.83)	41.4 (28.3;59.7)	Moderate	Important
						155/3879	26/10 000				

¹ 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 during 24 months.

² LTBI does not apply to the general population.

³ 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 yearly notification rate by a factor of 2.

⁴ High heterogeneity among studies ($I^2 = 84.4\%$), probably due to differences in background TB incidence.

⁵ Few events and wide 95% CI.

⁶ $I^2 = 88.1\%$, indicating high heterogeneity, probably due to differences in background TB prevalence; however, there is a trend across age groups and studies.

⁷ $I^2 = 16\%$.

Comparison with the general population for SR3

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

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

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 (9,17,18)	Cohort	Serious ¹	Not serious ²	Not serious	Serious ³	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 (9)	Cohort	Serious ¹	Not serious	Not serious	Serious ³	35/1464	13/10 000	18.39 (9.75;34.68)	22.6 (11.4;43.8)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10-14 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ¹	Not serious	Not serious	Serious ³	45/1340	13/10 000	25.83 (13.97;47.76)	32.3 (16.9;60.8)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5-15 YEARS VS GENERAL POPULATION											
3 (9,17,18)	Cohort	Serious ¹	Not serious ²	Not serious	Serious ³	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 (9)	Cohort	Serious ¹	Not serious	Not serious	Not serious	301/9380	13/10 000	24.68 (14.18;42.98)	30.8 (17.1;54.6)	Moderate	Important

¹ Ascertainment bias highly likely, 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).

² I² = 0%.

³ Few events and wide 95% CI.

Cumulative prevalence of active TB in household contacts, irrespective of baseline LTBI status, in high-TB incidence countries
Comparison with the general population (follow-up of 24 months)¹

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 (9,17,18, 23,28)	Cohort	Serious ²	Not serious ³	Not serious	Serious ⁴	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 (9)	Cohort	Serious ²	Not serious	Not serious	Serious ⁴	35/1464	26/10 000	9.2 (5.55;15.23)	21.3 (11.8;37)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 10-14 YEARS VS GENERAL POPULATION											
1 (9)	Cohort	Serious ²	Not serious	Not serious	Serious ⁴	45/1340	26/10 000	12.92 (8.0;20.86)	31 (18.2;51.6)	Low	Important
COMPARISON: HOUSEHOLD CONTACTS AGED 5-15 YEARS VS GENERAL POPULATION											
5 (9,17,18, 23,28)	Cohort	Serious ²	Serious ⁵	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 (9,23,28)	Cohort	Serious ²	Not serious ⁶	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				

¹ 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.

² 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.

³ Moderate heterogeneity among studies ($I^2 = 67.1\%$), probably due to differences in background TB incidence.

⁴ Few events and wide 95% CI.

⁵ High heterogeneity among studies ($I^2 = 87.5\%$), probably due to differences in background TB incidence.

⁶ Moderate heterogeneity among studies ($I^2 = 72.5\%$), probably due to differences in background TB incidence.

PICO2: What is the accuracy of WHO symptomatic screening to exclude active TB in individuals with HIV on antiretroviral treatment (ART)?

Population:	People living with HIV on ART	Background Active TB must be excluded before TB preventive treatment 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 people living with HIV before initiating TB preventive treatment. 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 TB preventive treatment and ART.
Intervention:	WHO-recommended four-symptom screening plus abnormal chest radiography. 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 → TB preventive treatment.	
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 \geq 100 per 100 000).	
Perspective:	Health system and public health.	
Subgroups:		

Assessment

	Judgement	Research evidence	Additional considerations																																																																	
Problem	Is the problem a priority? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 people living with HIV in 2015, representing one third of all HIV-related mortality. TB preventive treatment 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 TB preventive treatment is given.																																																																		
Test accuracy	How accurate is the test? <input type="radio"/> Very inaccurate <input type="radio"/> Inaccurate <input checked="" type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> Don't know	<p>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.</p> <table border="1"> <thead> <tr> <th rowspan="2">Subgroup</th> <th rowspan="2">Type of screening</th> <th rowspan="2">No. of studies</th> <th rowspan="2">Pooled sensitivity (%) (95% CI)</th> <th rowspan="2">Pooled specificity (%) (95% CI)</th> <th colspan="4">Negative predictive value for TB prevalence (%)</th> </tr> <tr> <th>1</th> <th>5</th> <th>10</th> <th>20</th> </tr> </thead> <tbody> <tr> <td rowspan="2">On ART</td> <td>Symptom screening alone</td> <td>7</td> <td>51.0 (28.4;73.2)</td> <td>70.7 (47.8;86.4)</td> <td>99.3</td> <td>96.5</td> <td>92.8</td> <td>85.2</td> </tr> <tr> <td>Symptom screening plus abnormal chest radiography</td> <td>2</td> <td>84.6 (69.7;92.9)</td> <td>29.8 (26.3;33.6)</td> <td>99.5</td> <td>97.4</td> <td>94.6</td> <td>88.6</td> </tr> <tr> <td rowspan="2">Not on ART</td> <td>Symptom screening alone</td> <td>15</td> <td>89.3 (82.6;93.6)</td> <td>27.2 (17.3;40.0)</td> <td>99.6</td> <td>98.0</td> <td>95.8</td> <td>91.1</td> </tr> <tr> <td>Symptom screening plus abnormal chest radiography</td> <td>5</td> <td>94.3 (76.2;98.8)</td> <td>20.1 (7.6;43.8)</td> <td>99.7</td> <td>98.5</td> <td>97.0</td> <td>93.4</td> </tr> <tr> <td>Pregnant women</td> <td>Symptom screening alone</td> <td>4</td> <td>27.1 (16.3;41.7)</td> <td>82.4 (79.1;85.2)</td> <td>99.1</td> <td>95.6</td> <td>91.1</td> <td>81.9</td> </tr> <tr> <td>Children</td> <td>Symptom screening alone</td> <td>1</td> <td>100 (76.8;100)</td> <td>4.3 (1.8;8.7)</td> <td>100</td> <td>100</td> <td>100</td> <td>100</td> </tr> </tbody> </table> <p>Two studies provided data on the combination of chest radiography and the four-symptom screening rule in PLHIV on ART. Any chest radiography abnormality was used in one study and chest radiography 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 chest radiography. The pooled sensitivity in the studies of the combination of abnormal chest radiography 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.</p> <p>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 chest radiography increases it by 0.2%.</p>	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	
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Children	Symptom screening alone	1	100 (76.8;100)	4.3 (1.8;8.7)	100	100	100	100																																																												

Balance of benefit vs harm	Do the benefits outweigh the harms? <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Equal <input type="radio"/> Uncertain	<p>The anticipated desirable effect of screening is correct identification of PLHIV who do not have active TB and are thus eligible for TB preventive treatment (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).</p> <p>Adults and adolescents on ART</p> <table border="1"> <thead> <tr> <th rowspan="2">Screening type</th> <th rowspan="2">Test accuracy</th> <th rowspan="2">Test results</th> <th colspan="3">Effect per 1000 individuals screened</th> <th rowspan="2">Quality of evidence</th> </tr> <tr> <th>Prevalence 1%</th> <th>Prevalence 5%</th> <th>Prevalence 10%</th> </tr> </thead> <tbody> <tr> <td rowspan="4">Symptom screening alone</td> <td rowspan="2">Sensitivity (%): 51.0 (28.4;73.2)</td> <td>True positive</td> <td>5 (3-7)</td> <td>26 (14-37)</td> <td>51 (28-73)</td> <td rowspan="2">⊕⊕○○ Low</td> </tr> <tr> <td>False negative</td> <td>5 (3-7)</td> <td>24 (13-36)</td> <td>49 (27-72)</td> </tr> <tr> <td rowspan="2">Specificity (%): 70.7 (47.8;86.4)</td> <td>True negative</td> <td>700 (473-855)</td> <td>672 (454-821)</td> <td>636 (430-778)</td> <td rowspan="2">⊕⊕○○ Low</td> </tr> <tr> <td>False positive</td> <td>290 (135-517)</td> <td>278 (129-496)</td> <td>264 (122-470)</td> </tr> <tr> <td rowspan="4">Symptom screening plus abnormal chest radiography</td> <td rowspan="2">Sensitivity (%): 84.6 (69.7;92.9)</td> <td>True positive</td> <td>8 (7-9)</td> <td>42 (35-46)</td> <td>85 (70-93)</td> <td rowspan="2">⊕⊕⊕○ Moderate</td> </tr> <tr> <td>False negative</td> <td>2 (1-3)</td> <td>8 (4-15)</td> <td>15 (7-30)</td> </tr> <tr> <td rowspan="2">Specificity (%): 29.8 (26.3;33.6)</td> <td>True negative</td> <td>295 (260-327)</td> <td>283 (250-314)</td> <td>268 (237-297)</td> <td rowspan="2">⊕⊕⊕⊕ High</td> </tr> <tr> <td>False positive</td> <td>695 (663-30)</td> <td>667 (636-700)</td> <td>632 (603-663)</td> </tr> </tbody> </table> <p>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 TB preventive treatment, while symptom screening plus abnormal chest radiography would wrongly put only two TB patients on preventive treatment.</p> <p>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 chest radiography were used, the number of HIV-positive people requiring TB investigations would increase (87 extra non-TB patients for every TB case identified).</p>				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)	True positive	5 (3-7)	26 (14-37)	51 (28-73)	⊕⊕○○ Low	False negative	5 (3-7)	24 (13-36)	49 (27-72)	Specificity (%): 70.7 (47.8;86.4)	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)	True positive	8 (7-9)	42 (35-46)	85 (70-93)	⊕⊕⊕○ Moderate	False negative	2 (1-3)	8 (4-15)	15 (7-30)	Specificity (%): 29.8 (26.3;33.6)	True negative	295 (260-327)	283 (250-314)	268 (237-297)	⊕⊕⊕⊕ High	False positive	695 (663-30)	667 (636-700)	632 (603-663)	<p>By adding abnormal chest radiography, 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 chest radiography could reduce concern of health workers about development of drug resistance.</p>
	Screening type	Test accuracy	Test results	Effect per 1000 individuals screened					Quality of evidence																																																	
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Evidence of accuracy	<p>What is the overall certainty of the evidence of test accuracy?</p> <p><input type="radio"/> Very low</p> <p><input checked="" type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>A systematic review was conducted, which identified two cross-sectional studies of the WHO-recommended four-symptom screening rule plus abnormal chest radiography. The studies involved 646 participants, of whom 39 (6.0%) had active TB.</p> <p>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.</p>	
Management effects	<p>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</p> <p><input checked="" type="radio"/> Major uncertainty</p> <p><input type="radio"/> Minor uncertainty</p>	<p>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).</p>	<p>The efficacy of preventive treatment might depend on confirmation of TB infection in an LTBI test.</p>
Values	<p>Is there important uncertainty about or variation in how many people value the main outcomes?</p> <p><input checked="" type="radio"/> Important uncertainty or variation</p> <p><input type="radio"/> No important uncertainty or variation</p>		<p>Addition of abnormal chest radiography increases burden on patients.</p> <p>Patients may value greater certainty in excluding active TB.</p>
Resources required	<p>How large are the resource requirements (costs)?</p> <p><input checked="" type="radio"/> Greater resource requirements</p> <p><input type="radio"/> Less resource requirements</p> <p><input type="radio"/> Neither greater nor less</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>		<p>More resources required, particularly if chest radiography is not available.</p> <p>Chest radiography would increase the number of HIV-positive people who undergo further investigations for TB.</p>

Cost effectiveness	<p>Does the cost-effectiveness of the test favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input type="radio"/> Favours the intervention <input checked="" type="radio"/> Varies <input type="radio"/> No included studies 		Cost-effectiveness could vary by region and health system infrastructure.
Equity	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Increased <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 		Impact on health equity depends on the setting (e.g. availability of chest radiography: could increase or decrease equity).
Acceptability	<p>Is the test acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 		Depends on availability of resources and infrastructure (e.g. electricity, radiologists).
Feasibility	<p>Is the test feasible to implement?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 		Varies significantly, mainly by setting, health system infrastructure and workload of HIV clinics.

Summary of judgements

Problem	Judgement							Implications
	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 variability			No important uncertainty or variability				
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 to exclude active TB in individuals with HIV on antiretroviral treatment (ART)?

Type of recommendation	Symptom screening alone <input type="checkbox"/>	Symptom screening plus chest radiography <input checked="" type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input type="checkbox"/>	Conditional <input checked="" type="checkbox"/>	
Recommendation	Chest radiography may be offered to people living with HIV and on ART and preventive treatment be given to those with no abnormal radiographic findings. (Conditional recommendation, low-quality evidence) <i>Remark: Chest radiography should not be a requirement for initiating preventive treatment.</i>		
Justification	<p>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 people living with HIV, regardless of whether they receive ART. It also noted the marginal potential benefits of adding abnormal chest radiography findings to the four-symptom screening rule. Moreover, increased use of chest radiography 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 chest radiography adds value only if it does not present a barrier for the provision of preventive treatment for people living with HIV.</p> <p>The GDG also noted that symptom screening with or without abnormal chest radiography findings would be acceptable to individuals and programme managers. Furthermore, the use of chest radiography could enhance the confidence of health care providers that active TB has been ruled out and reduce their concern for the development of drug resistance. The addition of chest radiography may incur costs to clients as well as inconvenience, as more clients will have to be investigated for TB and other diseases.</p>		
Subgroup considerations	Although no study was found of the additive role of chest radiography in testing pregnant women, the GDG noted that pregnant women living with HIV could also benefit, as long as good clinical practices are observed to prevent any significant risk to the fetus. 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	<p>Addition of abnormal chest radiographic findings to the symptom screening rule would complicate logistics, increasing the cost, workload, infrastructure and availability of qualified staff. The GDG noted that chest radiography should not be a requirement or a barrier for initiating TB preventive treatment in people living with HIV because of the need for additional resources, in view of the marginal gain in negative predictive value.</p> <p>People living with HIV who have any of the four symptoms or abnormal chest radiographic findings may have active TB and should be investigated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test. Other diseases that cause any of the four symptoms should be investigated in accordance with national guidelines and sound clinical practice. People living with HIV who present any of the four symptoms but in whom active TB is excluded by investigations may be considered for preventive treatment.</p> <p>The four-symptom screening method is recommended for all people living with HIV at every visit to a health facility or contact with a health worker. As combining chest radiography with symptom screening at every visit could represent a significant burden on the health system as well as on clients, it should be used only to exclude active TB before giving preventive treatment, with due respect for good clinical practice. The role of chest radiography in regular TB screening and its optimal frequency is uncertain. Local authorities should define its application and frequency on the basis of their local epidemiology, health infrastructure and resource availability. It is essential to ensure the availability of chest radiography and trained health care workers (e.g. radiologists) to implement the screening rule.</p>		
Monitoring and evaluation			
Research priorities	<ul style="list-style-type: none"> • 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 active TB 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 ¹	Serious ²	None ³	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 ¹	Serious ²	None ³	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 30-36

¹ Significant heterogeneity for sensitivity and specificity. Downgraded by 1.

² Wide confidence intervals. Downgraded by 1.

³ Possibility of publication bias not excluded, but not considered of sufficient concern to downgrade.

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

Population: Adults and adolescents with HIV on ART

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

Outcome	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 ¹	None ²	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 ²	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 30 and 35

¹ Imprecise estimate for sensitivity; downgraded by 1.

² Possibility of publication bias not excluded but not considered of sufficient concern to downgrade.

PICO3: What is the accuracy of symptomatic screening and/or chest radiography to exclude active TB in contacts of pulmonary TB cases without HIV in high TB incidence countries?

Population:	Contacts of pulmonary TB cases who are HIV-negative.	Background Active TB must be excluded before TB preventive treatment 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 chest radiography abnormality for excluding active TB before preventive treatment.
Intervention:	Symptom screening and/or chest radiography.	
Role of the test:	Rule out active TB before providing preventive treatment.	
Linked treatments:	Screening negative → TB preventive treatment.	
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? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 TB preventive treatment. A simple algorithm for excluding active TB is considered an essential component of programmatic LTBI management and could facilitate scaling-up of TB preventive treatment.																																																		
Test accuracy	How accurate is the test? <input type="radio"/> Very inaccurate <input type="radio"/> Inaccurate <input checked="" type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> Don't know	We updated a systematic review conducted in 2012 to determine the sensitivity and specificity of symptoms and chest radiography 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 <table border="1"> <thead> <tr> <th>Algorithm</th> <th>No. of studies</th> <th>Sensitivity</th> <th>Specificity</th> <th>False negative at screening</th> <th>Negative predictive value after negative screening</th> <th>False positive at screening</th> </tr> </thead> <tbody> <tr> <td>Chest radiography: any abnormality</td> <td>7</td> <td>0.941</td> <td>0.868</td> <td>12</td> <td>0.999</td> <td>1294</td> </tr> <tr> <td>Chest radiography: abnormality suggestive of TB</td> <td>6</td> <td>0.893</td> <td>0.922</td> <td>21</td> <td>0.998</td> <td>764</td> </tr> <tr> <td>Any cough</td> <td>10</td> <td>0.627</td> <td>0.775</td> <td>75</td> <td>0.990</td> <td>2205</td> </tr> <tr> <td>Cough \geq 2-3 weeks</td> <td>6</td> <td>0.382</td> <td>0.943</td> <td>124</td> <td>0.987</td> <td>559</td> </tr> <tr> <td>Any TB symptom</td> <td>11</td> <td>0.730</td> <td>0.766</td> <td>54</td> <td>0.993</td> <td>2303</td> </tr> <tr> <td>Any TB symptom plus any chest radiography abnormality</td> <td>*</td> <td>1.00</td> <td>0.701</td> <td>0</td> <td>1</td> <td>2930</td> </tr> </tbody> </table> <p>* No data could be obtained directly from the studies included in the systematic review; thus, the estimates were inferred from five studies of both chest radiography and symptom screening.</p>	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 \geq 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	*	1.00	0.701	0	1	2930	
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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 \geq 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	*	1.00	0.701	0	1	2841

* No data could be obtained from the studies included in the systematic review; thus, the estimates were inferred from five studies of both chest radiography and symptom screening.

The sensitivity and negative predictive value of chest radiography screening are high, especially if any chest radiography abnormality is used. Symptom screening is less sensitive, resulting in a lower negative predictive value.

In several studies, it was assumed that people without chest radiography 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 chest radiography 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.

Balance of benefits vs harm	<p>Do the benefits outweigh the harms?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Equal <input type="radio"/> Uncertain 	<p>One anticipated desirable effect of screening is correct identification of individuals who do not have active TB and are thus eligible for TB preventive treatment (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 TB preventive treatment immediately.</p> <p>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 TB preventive treatment. In contrast, use of any abnormal chest radiography finding would result wrongly in 12 TB patients being given preventive treatment. Use of the combination of any TB symptoms plus any chest radiography abnormal findings would result in no TB patients being given preventive treatment.</p> <p>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 chest radiography 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 chest radiography abnormal finding would increase the number of individuals requiring TB investigations to 15 extra non-TB patients for every TB case identified.</p>	
Certainty of evidence of test accuracy	<p>What is the overall certainty of the evidence of test accuracy?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>The quality of the evidence for any chest radiography 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 chest radiography abnormality plus any TB symptoms. Therefore, the overall certainty of the evidence is considered very low.</p>	

Certainty of the evidence of management's effects	<p>What is the overall certainty of the evidence of effects of management guided by test results?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Major uncertainty <input type="radio"/> Minor uncertainty 	<p>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).</p>	
Values	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Important uncertainty or variability <input type="radio"/> No important uncertainty or variability 		<p>Depends on health infrastructure and settings. Addition of abnormal chest radiography would increase burden on patients, although they might value an accurate test.</p>
Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Greater resource requirements <input type="radio"/> Less resource requirements <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A systematic literature review 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 chest radiography, 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.</p> <p>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.</p>	

Cost effectiveness	<p>Does the cost-effectiveness of the test favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input type="radio"/> Favours the intervention <input checked="" type="radio"/> Varies <input type="radio"/> No included studies 		Depends on the setting. It may be cost-effective in the long term by preventing development of drug-resistant TB.
Equity	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 		
Acceptability	<p>Is the test acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 		Depends on setting and availability of chest radiography.
Feasibility	<p>Is the test feasible to implement?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 		Depends on setting and availability of chest radiography and human resources.

Summary of judgements

Problem	Judgement							Implications
	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 variability			No important uncertainty or variability				
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 chest radiography to exclude active TB in contacts of pulmonary TB cases without HIV in high TB incidence countries?

Type of recommendation	Any chest radiography abnormality <input type="checkbox"/>	Chest radiography abnormality suggestive of TB <input type="checkbox"/>	Any cough <input type="checkbox"/>	Cough \geq 2-3 week <input type="checkbox"/>	Any TB symptom <input type="checkbox"/>	Any TB symptom plus any chest radiography abnormality <input checked="" type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input type="checkbox"/>			Conditional <input checked="" type="checkbox"/>			
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 \geq 5 years and other at-risk groups before preventive treatment. (<i>Conditional recommendation, very low-quality evidence</i>)						
Justification	Overall, the GDG agreed that the potential benefits of screening for active TB with the combination of any chest radiography 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 chest radiography would be acceptable for individuals and programme managers. Furthermore, the use of chest radiography 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 chest radiography 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 chest radiography 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. Chest radiography and trained health care workers (e.g. radiologists) must be available to implement the screening rule. Where chest radiography 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 chest radiography).						

GRADE tables

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

Index test: any abnormality in chest radiography| Reference test: Sputum culture and/or smear

Place of testing: Triage

Test-treatment pathway: chest radiography 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 ¹	Not serious ²	Not serious ³	Not serious ⁴	None ⁵	Prevalence (2%): 1 882 (1 716;1 954) Prevalence (5%): 4 705 (4 290;4 885)	⊕⊕⊕○ 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 ¹	Not serious ²	Not serious ³	Not serious ⁴	None ⁵	Prevalence (2%) : 85 064 (78 106;89 866) Prevalence (5%): 82 460 (75 715;87 115)	⊕⊕⊕○ Moderate
False positives (patients incorrectly classified as having active TB)								Prevalence (2%) : 12 936 (8 134;19 894) Prevalence (5%): 12 540 (7 885;19 285)	

Studies included: references 37,41,44,46-49

¹ Limitations in study design (see QUADAS-2): High risk of selection bias in one study (37). 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).

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

³ Inconsistency: Little heterogeneity in sensitivity or specificity (from visual inspection of 95% CIs).

⁴ Imprecision: Precise estimates for sensitivity and specificity.

⁵ 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 active TB in contacts of pulmonary TB cases 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 ¹	Not serious ²	Not serious ³	Not serious ⁴	None ⁵	Prevalence (2%): 1 460 (1 282;1 608) Prevalence (5%): 3 650 (3 205;4 020)	⊕⊕○○ Low
False negatives (patients incorrectly classified as not having active TB)								Prevalence (2%): 540 (392;718) Prevalence (5%): 1 350 (980;1 795)	
True negatives (patients without active TB)	11 studies; 357 609 patients	Cross-sectional (cohort type)	Very serious ¹	Not serious ²	Serious ³	Serious ⁴	None ⁵	Prevalence (2%): 74 970 (60 074;85 260) Prevalence (5%): 72 675 (58 235;82 650)	⊕○○○ Very low
False positives (patients incorrectly classified as having active TB)								Prevalence (2%): 23 030 (12 740;37 926) Prevalence (5%): 22 325 (12 350;36 765)	

From references 37–47

¹ Limitations in study design (see QUADAS-2): High risk of selection bias in one study (37) 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).

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

³ Inconsistency: moderate heterogeneity for sensitivity and significant heterogeneity for specificity (based on visual inspection of 95% CIs); downgrading on specificity.

⁴ Imprecision: precise estimates for sensitivity and imprecise estimate for specificity.

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

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

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 Mycobacterium 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? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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.	

Balance of effects	<p>Do the benefits outweigh the harm?</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> No</p> <p><input type="radio"/> Equal</p> <p><input type="radio"/> Uncertain</p>	<p>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 people living with HIV, 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, I² = 64.4%) and 2.03 (95% CI 1.18;3.50, 5 studies, I² = 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.</p> <table border="1" data-bbox="497 387 1722 608"> <thead> <tr> <th rowspan="2">Population</th> <th colspan="2">TST</th> <th colspan="2">IGRA</th> </tr> <tr> <th>Pooled RR</th> <th>I² (p value)</th> <th>Pooled RR</th> <th>I² (p value)</th> </tr> </thead> <tbody> <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>People living with HIV (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> </tbody> </table> <p>There was little evidence for specific at-risk populations. Two studies were conducted in people living with HIV, and the pooled estimates were imprecise.</p>	Population	TST		IGRA		Pooled RR	I ² (p value)	Pooled RR	I ² (p value)	All populations (5 studies)	1.49 (0.79;2.80)	64.4% (0.024)	2.03 (1.18;3.50)	49.6% (0.094)	People living with HIV (2 studies)	1.64 (0.24;11.18)	77.4% (0.035)	4.07 (0.18;92.72)	78.7% (0.030)	
Population	TST			IGRA																		
	Pooled RR	I ² (p value)	Pooled RR	I ² (p value)																		
All populations (5 studies)	1.49 (0.79;2.80)	64.4% (0.024)	2.03 (1.18;3.50)	49.6% (0.094)																		
People living with HIV (2 studies)	1.64 (0.24;11.18)	77.4% (0.035)	4.07 (0.18;92.72)	78.7% (0.030)																		
Certainty of evidence	<p>What is the overall certainty of the evidence of effects?</p> <p><input checked="" type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>																					
Values	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <p><input checked="" type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	<p>No evidence retrieved.</p>																				

Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Greater resource requirements with the intervention <input type="radio"/> Less resource requirements with the intervention <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't Know 	<p>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.</p>	
Cost effectiveness	<p>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input type="radio"/> Favours the intervention <input checked="" type="radio"/> Uncertain <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>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.</p> <p>Six cost evaluations were conducted among immunocompromised people (including people living with HIV) 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.</p> <p>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.</p>	<p>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.</p>
Equity	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't Know 	<p>No evidence retrieved.</p>	<p>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.</p>

Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <p> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't Know </p>	No evidence retrieved.	<p>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.</p>
Feasibility	<p>Is the intervention feasible to implement?</p> <p> <input type="radio"/> No <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't Know </p>		<p>Depends on the availability of resources and tests.</p> <p>IGRA: Phlebotomy is required, particularly for very young children, and sophisticated laboratory infrastructure, technical expertise and expensive equipment are required.</p> <p>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.</p> <p>Both tests have been available for many years and are used widely in many countries.</p>

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 variability			No important uncertainty or variability				
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-gamma release assays be used as an alternative to tuberculin skin tests to identify individuals most at risk of progression from LTBI to active TB in high TB incidence settings?

Recommendation	In favour of <input checked="" type="checkbox"/>	Against <input type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input checked="" type="checkbox"/>	Conditional <input type="checkbox"/>	
Recommendation	<p>Either a TST or IGRA can be used to test for LTBI. (<i>Strong recommendation, very low-quality evidence</i>) <i>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.</i></p>		
Justification	<p>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.</p> <p>The GDG also noted that equity and access could affect the choice and type of test used. The preferences of clients and programmes are, however, affected by several factors, such as the requirement for sophisticated laboratory infrastructure (e.g. for IGRA) and possible additional costs for clients (e.g. for travel) and programmes (e.g. for building and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages.</p> <p>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.</p> <p>The GDG cautioned that imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as people living with HIV. The GDG noted the importance of the tests for identifying recent conversion from a negative to a positive result, particularly among contacts of people with pulmonary TB, which is good practice for initiating TB preventive treatment. Nevertheless, recent studies among health care workers tested serially for LTBI in the USA showed that conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRA than with TST. Thus, sound clinical judgement must be used in interpreting the results of these tests when used serially.</p> <p>The GDG recommended that LTBI testing should not be a requirement for initiating TB preventive treatment for people living with HIV and child household contacts aged < 5 years, particularly in countries with a high TB incidence, given that clear benefits outweigh the risks. HIV-negative infant and child household contacts aged < 5 years and people living with HIV who have a negative LTBI test should be assessed case by case for their individual risk of exposure to TB and the added advantage of receiving preventive treatment.</p>		
Subgroup considerations			

Implementation considerations	<p>The GDG noted that the availability and affordability of the tests could determine which LTBI test is used. Other considerations include the structure of the health system, feasibility of implementation and infrastructure requirements. The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. Bacille Calmette-Guérin (BCG) vaccination plays a decisive role in reducing the specificity of TST, leading the choice towards IGRA-only strategies. The GDG noted, however, that the impact of BCG vaccination on the specificity of TST depends on the strain of vaccine used, the age at which the vaccine is given and the number of doses administered. When BCG is given at birth, as is the case in most parts of the world, it has a variable, limited impact on TST specificity. 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.</p> <p>IGRAs are more costly and more technically complex to perform than the TST. Operational difficulties should be considered in deciding which test to use. For example, IGRA requires a phlebotomy, which can be difficult, particularly in very young children, laboratory infrastructure, technical expertise and expensive equipment; however, only a single visit is required to obtain a result (although patients may have to make a second visit to learn the result). TST is less costly and can be performed in the field, but it requires a cold chain, two health care visits and training in intradermal injection, reading and interpretation.</p>
Monitoring and evaluation	
Research priorities	<p>New tests with better predictivity for progression from LTBI to active TB disease than current tests.</p> <p>Predictive performance of both tests in various at-risk populations.</p> <p>Cost-effectiveness studies under different conditions of burden and subgroups (e.g. children, people living with HIV).</p>

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

Review question: Among persons at high risk of LTBI 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?

SR Outcome: The predictive utility of the tuberculin skin test vs. the commercial interferon-gamma release assays 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 ($\geq 100/100\ 000$) 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. SR OUTCOME: PROGRESSION TO ACTIVE TB IN UNTREATED INDIVIDUALS									
5 (N = 7675 for TST, 7641 for IGRA) (51-55)	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 more to 36 more)	Very low ⊕○○○	Critical
B. SR OUTCOME (SUBGROUP ANALYSIS): PROGRESSION TO ACTIVE TB IN IMMUNOCOMPROMISED PEOPLE (INCLUDES HIV AND OTHER IMMUNOSUPPRESSIVE CONDITIONS)									
2 (N = 725 for TST, 710 for IGRA) (52, 54)	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. SR OUTCOME (SUBGROUP ANALYSIS) : PROGRESSION TO ACTIVE TB AMONG CONTACTS OF TB CASES									
1 (N = 1511 for TST, 1498 for IGRA) (55)	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 more to 69 more)	Very low ⊕○○○	Critical
D. SR OUTCOME (SUBGROUP ANALYSIS): PROGRESSION TO ACTIVE TB AMONG TB HEALTH CARE WORKERS									
1 (N = 195 for TST, 189 for IGRA) (53)	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. SR OUTCOME (SUBGROUP ANALYSIS): PROGRESSION TO ACTIVE TB AMONG ADOLESCENTS IN A HIGH-INCIDENCE SETTING									
1 (N = 5244 for both tests) (51)	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 more to 21 more) IGRA 10 more per 1000 (3 more 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 there were few studies 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 for 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 predictive utility. 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 predictive utility.

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 predictive utility.

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 people living with HIV 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? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't Know	Uptake of LTBI treatment is still suboptimal: only 38% of people living with HIV were newly enrolled in care in 2015 and 7.1% of child household contacts < 5 years started on preventive treatment. A systematic review (56) 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.	

Balance of effects	Do the benefits outweigh the harms? <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Uncertain <input type="radio"/> Equal	<table border="1"> <thead> <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> </thead> <tbody> <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 fewer 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 fewer 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 more 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 more to 671 more)</td> </tr> </tbody> </table> <p>A systematic review covered 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 radiography abnormalities suggestive of TB. In the same study, higher treatment adherence rate and fewer adverse events were observed in children given 3-4RH than in those given 9H.</p>	Outcome	3-4RH	6H/9H	Relative effect (RR) (95% CI)	Difference (95% CI)	Incidence of active TB (1 RCT)	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318-0.762)	122 fewer per 1000 (from 57 fewer to 164 fewer)	Adverse events (1 RCT)	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197-0.559)	83 fewer per 1000 (from 55 fewer to 100 fewer)	Adverse events (1 observational study)	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)	Completion rate (1 RCT)	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01-1.14)	60 more per 1000 (from 9 more to 121 more)	Completion rate (1 observational study)	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70-3.43)	389 more per 1000 (from 193 more to 671 more)	
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Certainty of evidence	What is the overall certainty of the evidence of effects? <input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		Although the quality of the evidence was low, data on adult populations support the benefits of 3RH.																														
Values	Is there important uncertainty about or variability in how much people value the main outcomes? <input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> No important uncertainty or variability	We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (Annex 3). 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".																															

Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input type="radio"/> Greater resource requirements with the intervention <input checked="" type="radio"/> Less resource requirements with the intervention <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't Know 	No evidence retrieved.	<p>Treatment is shorter with 3RH than 6H/9H.</p> <p>Use of 3RH would require fewer resources, particularly because the drug combination is already being used for treatment of active TB.</p>
Cost effectiveness	<p>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input checked="" type="radio"/> Favours the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	No evidence retrieved.	<p>Fewer resources required with 3RH, while its effectiveness is greater because of higher completion rate and safer profile.</p> <p>Cost-effectiveness favours 3RH in studies in adult populations.</p>
Equity	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't Know 	No evidence retrieved.	<p>The availability of more options would increase equity in accessing health services.</p>
Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't Know 	No evidence retrieved.	

Feasibility	<p>Is the intervention feasible to implement?</p> <p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't Know</p>	<p>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 twice daily, but there are very few studies and limited clinical experience with this combination (57).</p>	<p>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.</p>
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Summary of judgements

Problem	Judgement							Implications
	No		Equal	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 variability			No important uncertainty or variability				
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 <input checked="" type="checkbox"/>	Against <input type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input checked="" type="checkbox"/>	Conditional <input type="checkbox"/>	
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. (<i>Strong recommendation, low-quality evidence</i>)		
Justification	<p>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.</p> <p>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.</p> <p>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 variability 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.</p>		
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 people living with HIV 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

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-4-month daily rifampicin + isoniazid	6-9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
"RADIOLOGICAL" TB DISEASE: (58) (FOLLOW UP: 3-7 YEARS TO 7-11 YEARS; ASSESSED WITH: CHEST RADIOGRAPHY)												
1	RCT	Serious ¹	Not serious	Serious ²	Not serious	None	26/220 (11.8%)	48/200 (24.0%)	RR 0.492 (0.318-0.762)	122 fewer per 1000 (from 57 fewer to 164 fewer)	⊕⊕○○ Low	Critical
MORTALITY												
0									Cannot be estimated		-	Important
ADVERSE EVENTS: (58) (FOLLOW UP: 3-7 YEARS TO 7-11 YEARS; ASSESSED BY RECOGNITION OF SYMPTOMS AND ELEVATED LIVER ENZYMES)												
1	RCT	Very serious ^{1,3}	Not serious	Serious ⁴	Not serious	None	27/650 (4.2%)	25/200 (12.5%)	RR 0.332 (0.197-0.559)	83 fewer per 1000 (from 55 fewer to 100 fewer)	⊕○○○ Very low	Critical
ADVERSE EVENTS: (59) (FOLLOW UP: MEDIAN 97-197 DAYS; ASSESSED WITH: LIVER TOXICITY TEST AND CLINICAL)												
1	Observational	Serious ⁵	Not serious	Serious ⁴	Serious ⁶	None	1/220 (0.5%)	5/264 (1.9%)	RR 0.24 (0.03-2.04)	14 fewer per 1000 (from 18 fewer to 20 more)	⊕○○○ Very low	Critical
COMPLETION RATE: (58) (FOLLOW UP: 3-7 YEARS TO 7-11 YEARS)⁹												
1	RCT	Serious ⁷	Not serious	Serious ⁴	Not serious	None	220/238 (92.4%)	200/232 (86.2%)	RR 1.07 (1.01-1.14)	60 more per 1000 (from 9 more to 121 more)	⊕⊕○○ Low	Critical

No. of studies	Quality assessment						No. of patients		Effect		Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-4-month daily rifampicin + isoniazid	6-9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
COMPLETION RATE: (60) (ASSESSED FROM: COMPLETING > 80% OF TREATMENT WITHOUT INTERRUPTION OF > 2 MONTHS)												
1	Observational studies	Serious ⁵	Not serious	Not serious	Serious ⁸	None	48/72 (66.7%)	29/105 (27.6%)	RR 2.41 (1.70-3.43)	389 more per 1000 (from 193 more to 671 more)	⊕○○○ Very low	Critical
DRUG-RESISTANT TB												
0									Cannot be estimated		-	Important

From references 58-60

¹ Although there was a risk of selection bias, the characteristics of the two groups were similar. Patients with poor compliance were not included in the analysis of treatment outcomes. Downgraded by one level.

² There was no clinical disease. The outcome reported was new radiography findings suggestive of possible active disease. No comparison with 6H. Downgraded by one level.

³ 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.

⁴ No comparison with 6H. Downgraded by one level.

⁵ Risk of bias because of non-comparability of the two groups. Downgraded by one level.

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

⁷ Lack of blinding. Medication adherence test performed at home by parents. Although there was a risk of selection bias, the characteristics of the two groups were similar. Downgraded by one level.

⁸ Wide 95% CI. Downgraded by one level.

⁹ 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: Should 3-month weekly rifapentine and isoniazid be offered as an alternative regimen to isoniazid monotherapy for treatment of LTBI in high TB incidence countries?

Problem	Individuals with LTBI who are at high risk for active TB disease.	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 people living with HIV 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.
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 \geq 100 per 100 000).	
Perspective:	Health system and public health.	

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't Know	Uptake of LTBI treatment is still suboptimal, with only 38% of people living with HIV newly enrolled in care and 7.1% of child household contacts < 5 years started on preventive treatment in 2015. A systematic review (56) 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 (67) 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? <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Equal <input type="radio"/> 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? <input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> 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	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> No important uncertainty or variability 	<p>We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (Annex 3). 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%.</p>	
Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Greater resource requirements with the intervention <input type="radio"/> Less resource requirements with the intervention <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't Know 	<p>No evidence retrieved.</p>	<p>Implementation of 3HP would require more resources, particularly if it is to be given under DOT.</p>
Cost effectiveness	<p>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</p> <ul style="list-style-type: none"> <input type="radio"/> Favours the comparison <input type="radio"/> Favours neither the intervention nor the comparison <input type="radio"/> Favours the intervention <input checked="" type="radio"/> Varies <input type="radio"/> No included studies 	<p>In a cost-effective analysis of 3HP in the USA (62), 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.</p>	<p>Varies in different settings depending on cost of the drug and mode of administration (DOT or self-administration).</p>

Equity	<p>What would be the impact on health equity?</p> <p><input type="radio"/> Reduced</p> <p><input checked="" type="radio"/> Increased</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't Know</p>	No evidence retrieved.	The availability of more options is generally considered to increase equity.
Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <p><input type="radio"/> No</p> <p><input type="radio"/> Yes</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't Know</p>	No evidence retrieved.	Acceptability varies by risk group and setting, including mode of administration (self-administration or DOT).
Feasibility	<p>Is the intervention feasible to implement?</p> <p><input type="radio"/> No</p> <p><input type="radio"/> Yes</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't Know</p>	<p>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.</p> <p>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.</p> <p>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.</p>	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

Problem	Judgement							Implications
	No		Equal	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 variability			No important uncertainty or variability				
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 LTBI in high-TB incidence countries?

Recommendation	In favour of <input checked="" type="checkbox"/>	Against <input type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input type="checkbox"/>	Conditional <input checked="" type="checkbox"/>	
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. (<i>Conditional recommendation, moderate-quality evidence</i>)		
Justification	<p>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.</p> <p>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.</p> <p>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.</p>		
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	<p>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.</p> <p>3HP should be prescribed with caution to people living with HIV 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.</p>		
Monitoring and evaluation	The GDG stressed the importance of recording and reporting on the provision and completion of TB preventive treatment according to standardized indicators, in order to monitor progress in implementation.		
Research priorities	<ul style="list-style-type: none"> • 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 LTBI in high-TB incidence countries?

Population: Adults with HIV

Comparison: 6 or 9 months of isoniazid monotherapy

Overall quality: high

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		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 ¹	Serious ²	None	26/534 (4.9%)	28/520 (5.4%)	RR 0.733 (0.234–2.295)	14 fewer per 1000 (from 41 fewer to 70 more)	⊕⊕⊕○ Moderate	Critical
ALL-CAUSE MORTALITY												
2	RCTs	Not serious	Not serious	Not serious ¹	Serious ²	None	23/535 (4.3%)	30/513 (5.8%)	RR 0.746 (0.438–1.270)	15 fewer per 1000 (from 16 more to 33 fewer)	⊕⊕⊕○ Moderate	Important
ANY ADVERSE EVENT (GRADE III OR IV)												
2	RCTs	Serious ³	Not serious	Not serious ¹	Not serious	None	39/535 (7.3%)	59/513 (11.5%)	RR 0.627 (0.426–0.921)	43 fewer per 1000 (from 9 fewer to 66 fewer)	⊕⊕⊕○ Moderate	Critical
HEPATOTOXICITY												
2	RCTs	Not serious ⁴	Not serious	Not serious ¹	Not serious	None	8/535 (1.5%)	30/513 (5.8%)	RR 0.256 (0.118–0.553)	44 fewer per 1000 (from 26 fewer to 52 fewer)	⊕⊕⊕⊕ High	Critical
DRUG-RESISTANT TB												
2	RCTs	Not serious	Not serious	Not serious ¹	Very serious ⁵	None	3/534 (0.6%)	1/520 (0.2%)	RR 2.001 (0.259–15.436)	2 more per 1000 (from 1 fewer to 28 more)	⊕⊕○○ Low	Important

COMPLETION RATE												
2	RCTs	Not serious	Not serious	Not serious ¹	Not serious	None	497/534 (93.1%)	397/520 (76.3%)	RR 1.255 (1.014-1.553)	195 more per 1000 (from 11 more to 422 more)	⊕⊕⊕⊕ High	Critical

From references 63 and 64

¹ 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.

² 95% CIs of both relative and absolute effect indicate appreciable benefit and harm with 3HP.

³ Both trials were open-label, which may have introduced bias in ascertainment of adverse events.

⁴ Although the trials were open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

⁵ Very low event rates. Upper limit of 95% 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 LTBI 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 ¹	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 ¹	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
ANY ADVERSE EVENTS (GRADE III OR IV)												
1	RCT	Serious ²	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 fewer to 283 fewer)	⊕⊕⊕○ Moderate	Critical

HEPATOTOXICITY												
1	RCT	Not serious ³	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 fewer to 274 fewer)	⊕⊕⊕⊕ High	Critical
DRUG-RESISTANT TB												
1	RCT	Not serious	Not serious	Not serious	Very serious ⁴	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 more to 482 more)	⊕⊕⊕⊕ High	Critical

From reference 63

¹ 95% CIs of both relative and absolute effect indicate appreciable benefit and harm with 3HP.

² The trial was open-label, which may have introduced bias in ascertainment of adverse events.

³ 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.

⁴ 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 LTBI in high-TB incidence countries?

Population: Adults without HIV

Comparison: 6 or 9 months of isoniazid monotherapy

Overall quality: moderate

No. of studies	Study design	Quality assessment					No. of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month RPT+isoniazid	6 or 9 months' isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1	RCT	Not serious	Not serious	Serious ¹	Not serious ²	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179-1.074)	2 fewer per 1000 (from 0 fewer to 3 fewer)	⊕⊕⊕○ Moderate	Critical
ALL-CAUSE MORTALITY												
1	RCT	Not serious	Not serious	Serious ¹	Not serious ³	None	31/3986 (0.8%)	39/3759 (1.0%)	RR 0.740 (0.462-1.183)	3 fewer per 1000 (from 2 more to 6 fewer)	⊕⊕⊕○ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1	RCT	Serious ⁴	Not serious	Serious ¹	Not serious	None	229/4040 (5.7%)	244/3759 (6.5%)	RR 0.873 (0.733-1.040)	8 fewer per 1000 (from 3 more to 17 fewer)	⊕⊕○○ Low	Critical
HEPATOTOXICITY												
1	RCT	Not serious ⁵	Not serious	Serious ¹	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099-0.268)	23 fewer per 1000 (from 20 fewer to 25 fewer)	⊕⊕⊕○ Moderate	Critical
DRUG-RESISTANT TB												
1	RCT	Not serious	Not serious	Serious ¹	Not serious ³	None	1/3986 (0.0%)	2/3745 (0.1%)	RR 0.470 (0.043-5.179)	0 fewer per 1000 (from 1 fewer to 2 more)	⊕⊕⊕○ Moderate	Important

COMPLETION RATE												
1	RCT	Not serious	Not serious	Serious ¹	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159-1.221)	131 more per 1000 (from 110 more to 153 more)	⊕⊕⊕⊖ Moderate	Critical

From reference 65

¹ 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.

² 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.

³ Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. Not downgraded.

⁴ The open-label design of the trial may have introduced ascertainment bias. Downgraded by one level.

⁵ Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

Question: Should a 3-month regimen of weekly rifapentine plus isoniazid be offered as an alternative regimen to daily isoniazid monotherapy for treatment of LTBI 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 ¹	Not serious ²	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007-2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	⊕⊕⊕⊖ Moderate	Critical
ALL-CAUSE MORTALITY												
1	RCT	Not serious	Not serious	Serious ¹	Not serious ³	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009-3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	⊕⊕⊕⊖ Moderate	Important
ANY ADVERSE EVENT (GRADE III OR IV)												
1	RCT	Serious ⁴	Not serious	Serious ¹	Not serious ³	None	7/539 (1.3%)	8/493 (1.6%)	RR 0.875 (0.320-2.396)	2 fewer per 1000 (from 11 fewer to 23 more)	⊕⊕⊖⊖ Low	Critical

HEPATOTOXICITY												
1	RCT	Not serious ⁵	Not serious	Serious ¹	Not serious	None	0/539 (0.0%)	0/493 (0.0%)	Cannot be estimated	0 fewer per 1000 (from 4 fewer-4 more)	⊕⊕⊕○ Moderate	Critical
DRUG-RESISTANT TB												
0									Cannot be estimated		-	Important
COMPLETION RATE												
1	RCT	Not serious	Not serious	Serious ¹	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030-1.153)	72 more per 1000 (from 24 more to 124 more)	⊕⊕⊕○ Moderate	Critical

From reference 66

- ¹ 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.
- ² 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.
- ³ Although the 95% CI of the RR is wide, there were few events, and the CI of the absolute effect is narrow. Not downgraded.
- ⁴ The open-label design of the trial may have introduced ascertainment bias.
- ⁵ Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

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

Problem	Contacts of people with MDR or rifampicin-resistant TB.	Background People who have been in close contact with a TB case and who have become infected with <i>M. tuberculosis</i> are at high risk of progression to active disease, especially in the first 2 years after infection. Although TB preventive treatment is part of many TB control programmes, isoniazid monotherapy is unlikely to be effective in contacts of MDR-TB cases. In 2014, a guideline development group convened by WHO reviewed the evidence on use of preventive treatment of contacts of people with MDR-TB but could not make a recommendation because of the limited quality of the evidence. Rifampicin-resistant TB is considered a proxy for MDR-TB.
Option:	Tailored preventive treatment.	
Comparison:	No treatment (only follow-up observation).	
Main outcomes:	Incidence of active TB disease, incidence of MDR-TB, mortality, adverse events.	
Setting:	High- and low-TB incidence countries.	
Perspective:	Health system and public health.	

Assessment

	Judgement	Research evidence	Additional considerations																																																			
Problem	Is the problem a priority? <input type="radio"/> No <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Drug-resistant TB continues to threaten global TB control, remains a major public health concern and poses a global health security risk. An estimated 580 000 people developed MDR or rifampicin-resistant TB in 2015, and 250 000 people died as a result (67). Prevention of MDR-TB would reduce the global burden and also address demands from individuals to be protected against development of MDR-TB.																																																				
Balance of effects	Do the benefits outweigh the harm? <input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Equal <input type="radio"/> Uncertain	<p>We conducted a systematic review of the effectiveness of preventive treatment for contacts of patients with MDR or rifampicin-resistant TB. The review covered 10 studies with control groups, of which five found no TB case in either group. The table below summarizes the results after exclusion of studies with < 20 participants who completed preventive TB treatment and those on isoniazid monotherapy.</p> <table border="1"> <thead> <tr> <th>Outcomes</th> <th>Reference</th> <th>Intervention</th> <th>Control</th> <th>Relative effect (OR) (95% CI)</th> <th>Difference (95% CI)</th> <th>Follow-up</th> </tr> </thead> <tbody> <tr> <td rowspan="4">Incidence of active TB</td> <td>68</td> <td>2/41 (4.9%)</td> <td>13/64 (20.3%)</td> <td>0.20 (0.04-0.94)</td> <td>154 fewer per 1000 (273 fewer to 36 fewer)</td> <td>30 months</td> </tr> <tr> <td>69</td> <td>0/93 (0%)</td> <td>3/15 (20%)</td> <td>0.02 (0.00-0.39)</td> <td>200 fewer per 1000 (403 fewer to 3 more)</td> <td>36 months</td> </tr> <tr> <td>70</td> <td>0/21 (0%)</td> <td>0/10 (0%)</td> <td>-</td> <td>0 more per 1000 (138 fewer to 138 more)</td> <td>12 months</td> </tr> <tr> <td>71</td> <td>0/30 (0%)</td> <td>0/166 (0%)</td> <td>-</td> <td>0 more per 1000 (45 fewer to 45 more)</td> <td>≤ 9 years</td> </tr> <tr> <td rowspan="3">Incidence of MDR-TB</td> <td>69</td> <td>0/93 (0%)</td> <td>3/15 (20%)</td> <td>0.02(0.00-0.39)</td> <td>200 fewer per 1000 (403 fewer to 3 more)</td> <td>36 months</td> </tr> <tr> <td>70</td> <td>0/21 (0%)</td> <td>0/10 (0%)</td> <td>-</td> <td>0 more per 1000 (138 fewer to 138 more)</td> <td>12 months</td> </tr> <tr> <td>71</td> <td>0/30 (0%)</td> <td>0/166 (0%)</td> <td>-</td> <td>0 more per 1000 (45 fewer to 45 more)</td> <td>≤ 9 years</td> </tr> </tbody> </table> <p>Common adverse events included gastrointestinal symptoms, muscle or joint pain, headache, dizziness and hepatitis. In four studies, ≥ 50% of participants experienced at least one adverse event. Bamrah et al. (69) reported no serious adverse events, defined as hospitalization or irreversible morbidity, attributable to fluoroquinolone-based preventive treatment. The median proportion of participants who discontinued treatment because of adverse events in all studies was 5.1% (IQR 1.9-30.2%). No study reported preventive treatment for contacts of rifampicin-resistant TB.</p>	Outcomes	Reference	Intervention	Control	Relative effect (OR) (95% CI)	Difference (95% CI)	Follow-up	Incidence of active TB	68	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04-0.94)	154 fewer per 1000 (273 fewer to 36 fewer)	30 months	69	0/93 (0%)	3/15 (20%)	0.02 (0.00-0.39)	200 fewer per 1000 (403 fewer to 3 more)	36 months	70	0/21 (0%)	0/10 (0%)	-	0 more per 1000 (138 fewer to 138 more)	12 months	71	0/30 (0%)	0/166 (0%)	-	0 more per 1000 (45 fewer to 45 more)	≤ 9 years	Incidence of MDR-TB	69	0/93 (0%)	3/15 (20%)	0.02(0.00-0.39)	200 fewer per 1000 (403 fewer to 3 more)	36 months	70	0/21 (0%)	0/10 (0%)	-	0 more per 1000 (138 fewer to 138 more)	12 months	71	0/30 (0%)	0/166 (0%)	-	0 more per 1000 (45 fewer to 45 more)	≤ 9 years	
Outcomes	Reference	Intervention	Control	Relative effect (OR) (95% CI)	Difference (95% CI)	Follow-up																																																
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Certainty of evidence	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>The overall quality of the evidence was very low because of very serious risks of bias and imprecision. In the study by Trieu et al. (71), active TB was ascertained during follow-up by checking cases identified in the TB registry. A meta-analysis was not conducted because of the heterogeneity of the drugs used.</p>	
Values	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> <input type="radio"/> Important uncertainty or variability <input type="radio"/> No important uncertainty or variability <input checked="" type="radio"/> Minimal uncertainty 	<p>We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (Annex 3). Data were available from 142 respondents. More than 80% of the respondents reported that they would strongly or somewhat prefer to receive preventive treatment or give it to their children if they were exposed to someone with MDR-TB disease in the household. The reasons for not preferring preventive treatment included: limited evidence on preventive treatment for MDR-TB and concern about side-effects and development of drug resistance.</p>	<p>There is uncertainty about the characteristics of respondents.</p>
Resources required	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> <input checked="" type="radio"/> Greater resource requirements with the intervention <input type="radio"/> Less resource requirements with the intervention <input type="radio"/> Neither greater nor less <input type="radio"/> Varies <input type="radio"/> Don't know 		

Cost effectiveness	<p>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</p> <p><input type="radio"/> Favours the comparison</p> <p><input type="radio"/> Favours neither the intervention nor the comparison</p> <p><input type="radio"/> Favours the intervention</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> No included studies</p>		<p>Providing preventive treatment could be cost-effective by preventing MDR-TB cases in settings with low transmission of MDR-TB. In settings with high risk of MDR-TB transmission, the potential benefit may wane and the cost-effectiveness becomes uncertain. The need for drug susceptibility testing, regimens used, risk of re-infection and adverse events could also affect cost-effectiveness.</p>
Equity	<p>What would be the impact on health equity?</p> <p><input type="radio"/> Reduced</p> <p><input checked="" type="radio"/> Increased</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>		
Acceptability	<p>Is the intervention acceptable to key stakeholders?</p> <p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>Some national or clinical guidelines already recommend preventive treatment for contacts of MDR-TB (72-74).</p>	<p>Preventive treatment could be acceptable, particularly to patients and health care workers. The intervention may not be acceptable in some settings, particularly to programme managers for fear of development of XDR-TB and little experience in using TB preventive treatment for drug-susceptible TB.</p>
Feasibility	<p>Is the intervention feasible to implement?</p> <p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>		

Summary of judgements

Problem	Judgement							Implications
	No		Equal	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 variability		Minimal uncertainty	No important uncertainty or variability				
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 preventive treatment be recommended for contacts of patients with MDR or rifampicin-resistant TB?

Recommendation	In favour of <input checked="" type="checkbox"/>	Against <input type="checkbox"/>	No recommendation <input type="checkbox"/>
Strength of recommendation	Strong <input type="checkbox"/>	Conditional <input checked="" type="checkbox"/>	
Recommendation	<p>In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. <i>(Conditional recommendation, very low-quality evidence)</i></p> <p><i>Remarks</i> The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events. The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV). The drugs should be selected according to the drug susceptibility profile of the source case. Confirmation of infection with LTBI tests is required. This recommendation must not affect on-going placebo-controlled clinical trials of MDR-TB contacts on ethical grounds. The results of such clinical trials are crucial for updating this recommendation. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.</p>		
Justification	<p>Overall, the GDG judged that the potential benefits of targeted preventive treatment for MDR-TB contacts based on individual risk assessments outweigh the harm but acknowledged uncertainty about the efficacy of the intervention due to the lack of RCTs. It also noted that provision of preventive treatment for MDR-TB contacts would be acceptable, particularly to patients and health care workers. The GDG stressed that treatment should be given to selected individuals after a careful risk assessment, including intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the index case and potential adverse events. It should be given only to household contacts at high risk (e.g. children, people on immunosuppressive therapy and people living with HIV). Confirmation of infection by LTBI testing is required before individualized treatment is initiated.</p>		
Subgroup considerations			
Implementation considerations	<p>Close monitoring and treatment adherence Close monitoring of adverse events and adherence to treatment is essential. The types of adverse events depend on the drugs used. Common adverse events associated with each drug are listed in the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (75). Adverse effects should be monitored according to the WHO framework for monitoring and managing the safety of drugs against active TB (76). The GDG reiterated that strict clinical observation and close monitoring for active TB disease based on sound clinical practice and national guidelines for at least 2 years is required, regardless of the provision of preventive treatment. Consideration should also be given to interactions with antiretroviral, immunosuppressant and other drugs when providing TB preventive treatment.</p> <p>Informed consent As the recommendation is based on very low-quality evidence, clients must be given detailed information about the benefits and harms of the preventive treatment and asked for explicit informed consent. In view of the uncertainty about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practice in similar situations.</p>		

	<p>Selection of drug regimen The regimen of preventive treatment of MDR-TB contacts should be based on reliable information on the drug resistance profile of the source case. Later-generation fluoroquinolones (e.g. levofloxacin and moxifloxacin) are considered to be important components of a preventive treatment regimen unless the strain of the source case is resistant to them. Although there has been concern about the use of fluoroquinolones in children because retardation of cartilage development was shown in animals, similar effects have not been demonstrated in humans. There is limited evidence for the duration of treatment, and this should be based on clinical judgement. The regimens used in the studies conducted so far were given for 6, 9 and 12 months.</p> <p>Resources and feasibility For a programmatic approach, all the necessary resources should be in place, including for quality-assured testing for drug susceptibility, the necessary medications and a system for close monitoring of harm and adverse events. The feasibility of providing preventive treatment should be carefully assessed according to the availability of resources and the history and status of preventive treatment for drug-susceptible TB.</p>
Monitoring and evaluation	
Research priorities	<ul style="list-style-type: none"> • Adequately powered RCTs to update the recommendation on preventive treatment for MDR-TB contacts. • Effectiveness and safety of preventive treatment for MDR contacts under operational conditions. • Further evidence on risk of progression to active TB among MDR contacts to understand the benefits of preventive treatment.

GRADE table

Question: Should preventive treatment be recommended for contacts of patients with MDR or rifampicin-resistant TB?

Overall quality: very low

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

MORTALITY												
0	No evidence available									Cannot be estimated	-	Important
ADVERSE EVENTS												
0	No evidence available									Cannot be estimated	-	Critical
DEVELOPMENT OF DRUG RESISTANCE												
0	No evidence available											Important

From references 68-71. Five studies in which fewer than 20 participants completed preventive TB treatment were excluded, as was a study by Kristi (77), in which only isoniazid monotherapy was used.

¹ Risk of bias in selection of the control group, and confounders were not adjusted for in any study. Downgraded by two levels.

² Small sample sizes and wide 95% CIs. Downgraded by two levels.

³ Reference 68

⁴ Reference 69

⁵ Reference 70

⁶ Reference 71

⁷ The study by Shaaf et al. (68) was excluded as the incidence of MDR-TB was not reported.

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