WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment

ANNEX 3

GRADE evidence-to-decision tables

THE END TB STRATEGY

World Health Organization

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Annex 3. GRADE evidence-to-decision tables

World Health Organization

WHO/UCN/TB/2020.3

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This publication forms part of the WHO guideline entitled *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014)**.**

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

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? ○ No ● Yes ○ Varies ○ Don't know	Globally in 2015, there were an estimated 10.4 million incident cases of TB and 1.8 million deaths from TB. Management of LTBI is critical in order to end the global TB epidemic, as stated in the WHO End TB Strategy. Active TB must be excluded before 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? ● Yes ○ No ○ They are equal ○ Uncertain	We updated three systematic reviews conducted for the previous LTBI guidelines, focusing on household contacts. The first review addressed the prevalence of LTBI among household contacts by age group, the second the risk of progression from LTBI to active TB among household contacts and the third the cumulative prevalence of active TB among household contacts, irrespective of baseline LTBI status. In most of the studies, prevalent TB cases were those identified at the baseline visit, and those identified later were counted as incident cases. The incidence of TB therefore depended on the timing of the baseline visit relative to the diagnosis of the index case; focusing on incident TB cases, therefore, may introduce bias. In the second and 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.	

Balance of effects

Pooled estimates of prevalence of LTBI among household contacts by age stratum as compared with children < 5 years in high-TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000)

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

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

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

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

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

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

The review consistently showed that older household contacts 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.

<table>
<tr>
<td>Balance of effects</td>
<td></td>
<td>
Pooled estimates of risk of development of active TB among household contacts stratified by age and baseline LTBI status compared to the general population.
<table>
<tr><th></th><th colspan="4">Baseline LTBI status positive</th><th colspan="4">Regardless of baseline LTBI status</th></tr>
<tr><th></th><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>Age (years)</th><th>No. of 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><th>Risk ratio</th></tr>
<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 (1 930)</td><td>25.86 (16.87-39.66)</td><td>5 (2 773)</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 (1 464)</td><td>18.39 (9.75-34.68)</td><td>1 (1 464)</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 (1 340)</td><td>25.83 (13.97-47.76)</td><td>1 (1 340)</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 (1 203)</td><td>8.22 (2.3-29.36)</td><td>3 (3 067)</td><td>24.11 (16.89-34.43)</td><td>5 (4 197)</td><td>6.29 (2.88-13.72)</td></tr>
<tr><td>≥15</td><td>1 (3 879)</td><td>30.74 (17.46-54.07)</td><td>2 (4 450)</td><td>13.35 (9.46-18.83)</td><td>1 (9 380)</td><td>24.68 (14.18-42.98)</td><td>3 (10 531)</td><td>11.67 (7.55-18.02)</td></tr>
</table>
The results showed that household contacts have substantially higher risk of active TB compared to the general population regardless of their age.
</td>
<td></td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>What is the overall certainty of the evidence of effects?
○ Very low
● Low
○ Moderate
○ High
○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
○ No important uncertainty or variability
● Minimal uncertainty</td>
<td>We conducted an online survey (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf) 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.</td>
<td>Concern about whether the respondents in the online survey correctly reflect the values of clients.</td>
</tr>
</table>

Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know		National programmes could build upon existing programmes for children < 5 years, which could reduce the additional resource requirements.
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies	A systematic review of the cost-effectiveness of management of LTBI was undertaken for the 2015 WHO LTBI guidelines. The review covered six studies 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.	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. A recent modelling study suggested that preventive treatment without LTBI testing is cost-effective for child contacts < 5 years old *(1)*.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know		

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

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Unknown**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No 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 ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(Conditional recommendation, low-quality evidence.)* *Remark: Appropriate clinical evaluation should include assessment of the intensity of and risk for exposure, the risk for development of active TB and/or ascertainment of infection by testing for LTBI.*		
Justification	The GDG agreed that, overall, the potential benefits of preventive treatment for household contacts outweigh the harm, regardless of age, given the high risk for development of active TB disease. The GDG also noted that the balance of benefits and harm depends on confirmation of infection by LTBI testing, and the benefits would be greater in household contacts with a positive LTBI test. There was 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. 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.		
Subgroup considerations			
Implementation considerations	In order to ensure that the benefits of preventive treatment outweigh the harm, careful clinical assessment of the intensity of and risk for exposure, of the risk for development of active TB and/or with LTBI testing are required. Active TB must be excluded before preventive treatment is given. It is important to provide support for adherence adapted to the local context to ensure completion of treatment. This may be particularly challenging for certain populations such as adolescents. The support should take into account their needs. National programmes should ensure the availability of tests and drugs and properly train health care workers to provide preventive treatment for household contacts of all ages.		
Monitoring and evaluation			
Research priorities	Methods to improve adherence and completion rate. Implementation research to improve effectiveness and efficiency of managing household contacts (e.g. household-based intervention to reduce barriers). Development of diagnostic tests with improved performance and predictive value for reactivation of TB. Durability of protection by preventive treatment in TB endemic settings.		

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 32/230	41/10 000 13/10 000	24.32 (0.73;811.02)	63 (–0.7;2187.1)	Very low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED 5–9 YEARS VS GENERAL POPULATION											
1 *(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 38/661	41/10 000 13/10 000	27.13 (17.47;54.07)	70.5 (21.3;220.7)	Low	Critical
COMPARISON: HOUSEHOLD CONTACTS AGED > 15 YEARS VS GENERAL POPULATION											
1 *(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] $I^2 = 0\%$.

[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.

PICO 2: 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 ≥ 100 per 100 000).	
Perspective:	Health system and public health.	
Subgroups:		

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
● Yes
○ Varies
○ Don't know</td><td>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.</td><td></td></tr>
<tr><td>Test accuracy</td><td>How accurate is the test?
○ Very inaccurate
○ Inaccurate
● Accurate
○ Very accurate
○ Varies
○ Don't know</td><td>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.

<table>
<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>
<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>
</table>

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.

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%.</td><td></td></tr>
</table>

Balance of benefit vs harm

Do the benefits outweigh the harms?

- ● Yes
- ○ No
- ○ Equal
- ○ Uncertain

The anticipated desirable effect of screening is correct identification of PLHIV who do not have active TB and are thus eligible for 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).

Adults and adolescents on ART

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

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

At a TB prevalence of 1%, symptom screening alone would require TB investigations for 58 extra non-TB patients for every TB case identified. Similarly, when symptom screening plus abnormal 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).

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.

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

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

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Test accuracy	**Very inaccurate**	**Inaccurate**	**Accurate**	**Very accurate**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of the evidence of test accuracy	**Very low**	**Low**	**Moderate**	**High**			**No incuded 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 incuded 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 ☐	Symptom screening plus chest radiography ☒	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
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)* *Remark: Chest radiography should not be a requirement for initiating preventive treatment.*		
Justification	Overall, the GDG agreed that the screening rule based on four symptoms is very useful for ruling out active TB before providing preventive treatment to 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. 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.		
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	Addition of abnormal chest radiographic findings to the symptom screening rule would complicate logistics, increasing the cost, workload, infrastructure and availability of qualified staff. The GDG noted that chest radiography should not be a requirement or a barrier for initiating TB preventive treatment in people living with HIV because of the need for additional resources, in view of the marginal gain in negative predictive value. People living with HIV who have any of the four symptoms or abnormal chest radiographic findings may have active TB and should be investigated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test. Other diseases that cause any of the four symptoms should be investigated in accordance with national guidelines and sound clinical practice. People living with HIV who present any of the four symptoms but in whom active TB is excluded by investigations may be considered for preventive treatment. The four-symptom screening method is recommended for all people living with HIV at every visit to a health facility or contact with a health worker. As combining chest radiography with symptom screening at every visit could represent a significant burden on the health system as well as on clients, it should be used only to exclude active TB before giving preventive treatment, with due respect for good clinical practice. The role of chest radiography in regular TB screening and its optimal frequency is uncertain. Local authorities should define its application and frequency on the basis of their local epidemiology, health infrastructure and resource availability. It is essential to ensure the availability of chest radiography and trained health care workers (e.g. radiologists) to implement the screening rule.		
Monitoring and evaluation			
Research priorities	• Performance and feasibility of the algorithms proposed in the present guidelines. • In particular, data on the screening rule for children and pregnant women.		

GRADE tables

Question: What is the performance of WHO-recommended four-symptom screening to exclude 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.

PICO 3: 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

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
● Yes
○ Varies
○ Don't know</td><td>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.</td><td></td></tr>
<tr><td>Test accuracy</td><td>How accurate is the test?
○ Very inaccurate
○ Inaccurate
● Accurate
○ Very accurate
○ Varies
○ Don't know</td><td>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>
<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>
<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 ≥ 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>
</table>
* 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.</td><td></td></tr>
</table>

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

Algorithm	No. of studies	Sensitivity	Specificity	False negative at screening	Negative predictive value after negative screening	False positive at screening
Chest radiography: any abnormality	7	0.941	0.868	30	0.996	1254
Chest radiography: abnormality suggestive of TB	6	0.893	0.922	54	0.994	741
Any cough	10	0.627	0.775	187	0.975	2136
Cough ≥ 2-3 weeks	6	0.382	0.943	309	0.967	542
Any TB symptom	11	0.730	0.766	135	0.982	2233
Any TB symptom plus any chest radiography abnormality	*	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	Do the benefits outweigh the harms? ● Yes ○ No ○ Equal ○ Uncertain	One anticipated desirable effect of screening is correct identification of individuals who do not have active TB and are thus eligible for 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. 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. 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.	
Certainty of evidence of test accuracy	What is the overall certainty of the evidence of test accuracy? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence for any 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.	

Certainty of the evidence of management's effects	What is the overall certainty of the evidence of effects of management guided by test results? ● Major uncertainty ○ Minor uncertainty	The studies included were not designed to assess the effects of management with different screening strategies on patient outcomes (e.g. active TB incidence, mortality, drug resistance).	
Values	Is there important uncertainty about or variability in how much people value the main outcomes? ● Important uncertainty or variability ○ No important uncertainty or variability		Depends on health infrastructure and settings. Addition of abnormal chest radiography would increase burden on patients, although they might value an accurate test.
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements ○ Less resource requirements ○ Neither greater nor less ○ Varies ○ Don't know	A systematic literature review 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. 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.	

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

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Test accuracy	**Very inaccurate**	**Inaccurate**	**Accurate**	**Very accurate**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of the evidence of test accuracy	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Certainty of the evidence of effects on management	**Major uncertainty**			**Minor uncertainty**				
Values	**Important uncertainty or 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 ☐	Chest radiography abnormality suggestive of TB ☐	Any cough ☐	Cough ≥ 2–3 week ☐	Any TB symptom ☐	Any TB symptom plus any chest radiography abnormality ☒	No recommendation ☐
Strength of recommendation	Strong ☐			Conditional ☒			
Recommendation	The absence of any symptoms and the absence of TB and of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other at-risk groups before preventive treatment. *(Conditional recommendation, very low-quality evidence)*						
Justification	Overall, the GDG agreed that the potential benefits of screening for active TB with the combination of any 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? ○ No ● Yes ○ Varies ○ Don't Know	Currently, LTBI testing is not required before provision of preventive treatment in high-TB incidence countries. It can identify individuals who would benefit most from LTBI treatment and is used in some high-incidence countries. Lack of availability of TST because of the global shortage of purified protein derivative has been cited as a barrier to scaling-up of programmatic management of LTBI. The availability of an alternative test, IGRA, may facilitate scaling-up.	

<table>
<tr>
<td>Balance of effects</td>
<td>Do the benefits outweigh the harm?
● Yes
○ No
○ Equal
○ Uncertain</td>
<td>Five relevant studies of IGRA and TST in high-TB incidence countries were identified (N = 7769). All were prospective cohort studies of participants who received both TST and IGRA. Two were conducted in India and three in South Africa. The populations studied were 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, I^2 = 64.4%) and 2.03 (95% CI 1.18;3.50, 5 studies, I^2 = 49.6%) for IGRA. Although the pooled effect estimate for IGRA was slightly higher and the heterogeneity lower than for TST, the 95% CIs around the effect estimates overlapped and were imprecise.
<table>
<tr><th></th><th colspan="2">TST</th><th colspan="2">IGRA</th></tr>
<tr><th>Population</th><th>Pooled RR</th><th>I^2 (p value)</th><th>Pooled RR</th><th>I^2 (p value)</th></tr>
<tr><td>All populations
(5 studies)</td><td>1.49
(0.79;2.80)</td><td>64.4%
(0.024)</td><td>2.03
(1.18;3.50)</td><td>49.6%
(0.094)</td></tr>
<tr><td>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>
</table>
There was little evidence for specific at-risk populations. Two studies were conducted in people living with HIV, and the pooled estimates were imprecise.</td>
<td></td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High
○ No included studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
● Important uncertainty or variability
○ No important uncertainty or variability</td>
<td>No evidence retrieved.</td>
<td></td>
</tr>
</table>

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

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

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or 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 ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☒	Conditional ☐	
Recommendation	Either a TST or IGRA can be used to test for LTBI. *(Strong recommendation, very low-quality evidence)* *Remark: The availability and affordability of the tests will determine which will be chosen by clinicians and programme managers. Neither TST nor IGRA can be used to diagnose active TB disease nor for diagnostic workup of adults suspected of having active TB.*		
Justification	The GDG concluded that the comparison of TST and IGRA in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to active TB disease. The GDG noted that TST may require significantly fewer resources than IGRA and may be more familiar to practitioners in resource-constrained settings; however, recurrent global shortages and stock-outs of TST reduce its use in scaling up programmatic management of LTBI. The GDG also noted that equity and access could affect the choice and type of test used. The preferences of clients and programmes are, however, affected by several factors, such as the requirement for sophisticated laboratory infrastructure (e.g. for IGRA) and possible additional costs for clients (e.g. for travel) and programmes (e.g. for building and testing). The GDG strongly recommended the two tests as equivalent options, with relatively similar advantages and disadvantages. The GDG stressed that the global shortage of TST should be addressed urgently and called for more investment into research on novel tests for LTBI with better predictive value. The GDG cautioned that imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as people living with HIV. The GDG noted the importance of the tests for identifying recent conversion from a negative to a positive result, particularly among contacts of people with pulmonary TB, which is good practice for initiating TB preventive treatment. Nevertheless, recent studies among health care workers tested serially for LTBI in the USA showed that conversions from negative to positive and reversions from positive to negative are more commonly identified with IGRA than with TST. Thus, sound clinical judgement must be used in interpreting the results of these tests when used serially. The GDG recommended that LTBI testing should not be a requirement for initiating TB preventive treatment for people living with HIV and child household contacts aged < 5 years, particularly in countries with a high TB incidence, given that clear benefits outweigh the risks. HIV-negative infant and child household contacts aged < 5 years and people living with HIV who have a negative LTBI test should be assessed case by case for their individual risk of exposure to TB and the added advantage of receiving preventive treatment.		
Subgroup considerations			

Implementation considerations	The GDG noted that the availability and affordability of the tests could determine which LTBI test is used. Other considerations include the structure of the health system, feasibility of implementation and infrastructure requirements. The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. 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. 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.
Monitoring and evaluation	
Research priorities	New tests with better predictivity for progression from LTBI to active TB disease than current tests. Predictive performance of both tests in various at-risk populations. Cost–effectiveness studies under different conditions of burden and subgroups (e.g. children, people living with HIV).

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 (≥ 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? ○ No ● Yes ○ Varies ○ 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.	

<table>
<tr>
<td>Balance of effects</td>
<td>Do the benefits outweigh the harms?
● Yes
○ No
○ Uncertain
○ Equal</td>
<td>
<table>
<tr><th>Outcome</th><th>3–4RH</th><th>6H/9H</th><th>Relative effect (RR) (95% CI)</th><th>Difference (95% CI)</th></tr>
<tr><td>Incidence of active TB
(1 RCT)</td><td>26/220 (11.8%)</td><td>48/200 (24.0%)</td><td>RR 0.492
(0.318–0.762)</td><td>122 fewer per 1000
(from 57 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>
</table>
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.
</td>
<td></td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>What is the overall certainty of the evidence of effects?
○ Very low
● Low
○ Moderate
○ High
○ No included studies</td>
<td></td>
<td>Although the quality of the evidence was low, data on adult populations support the benefits of 3RH.</td>
</tr>
<tr>
<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
○ Important uncertainty or variability
● No important uncertainty or variability</td>
<td>We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf). Data were available from 142 respondents, of whom 59 had at least one child. The respondents were asked to rate the importance of each attribute of the LTBI treatment regimen on a five-point scale on which 5 is “very important” and 1 is “not important”. 90–100% of the respondents with children rated the following attributes as “very important” or “important” for their children: shorter duration, fewer side-effects, fewer visits to the clinic, easy to swallow and less frequent intake. Fewer respondents (78.0%) rated “no need for direct observed therapy (DOT)” as “very important” or “important”.</td>
<td></td>
</tr>
</table>

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

Feasibility	Is the intervention feasible to implement? ○ No ● Yes ○ Varies ○ Don't Know	Co-administration of rifampicin with protease inhibitors is not recommended. Rifampicin is known to significantly lower plasma concentrations of dolutegravir, and the dosing schedule might have to be increased to to twice daily, but there are very few studies and limited clinical experience with this combination *(57)*.	Drug interactions preclude its co-administration with protease inhibitors or nevirapine (e.g. infants born to HIV-positive mothers receiving nevirapine). Little concern about drug interactions in HIV-negative child contacts.

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't Know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or 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 ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☒	Conditional ☐	
Recommendation	Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence)*		
Justification	The GDG unanimously agreed that the benefits of 3RH outweigh the harm, given its safer profile, higher completion rate than with isoniazid monotherapy and the availability of child-friendly fixed-dose combinations of rifampicin and isoniazid. The GDG noted that, although the quality of the evidence was low, data on adult populations also support the benefits of 3RH. A systematic review of RCTs on preventive treatment options conducted in 2014 showed that the efficacy and the risk for hepatotoxicity are similar for 3RH and isoniazid monotherapy. The GDG noted that use of 3RH would require fewer resources, given the shorter duration of treatment, which would reduce the number of clinic visits required. It also suggested that the initial cost of use of 3RH would be low, as it is already being used for treatment of active TB. The GDG agreed that cost-effectiveness favours 3RH because of the higher completion rate, safer profile and fewer resources required. The GDG also noted that, although direct evidence for the cost-effectiveness of 3RH in children is limited, the cost-effectiveness of shorter preventive treatment including 3RH is supported by a body of evidence in adult populations. The GDG agreed that there is no important uncertainty or 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.		
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

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin + isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
"RADIOLOGICAL" TB DISEASE: *(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

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3–4-month daily rifampicin + isoniazid	6–9-month isoniazid monotherapy	Relative (95% CI)	Absolute (95% CI)		
COMPLETION RATE: *(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: In people of all ages at risk of active TB, does a 4-month daily rifampicin regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens?

Population:	In people of all ages at risk of active TB *in high TB burden settings*
Intervention:	A regimen with four months of daily rifampicin ("4R")
Comparison:	Another regimen (9-months of isoniazid alone [9H] for the studies identified and reviewed)
Main outcomes:	Outcomes scored as critical or important by the GDG were: active TB incidence, mortality, adverse events, treatment completion, emergence of drug resistance
Setting:	For this PICO question the GDG considered data from two phase 3 randomized controlled trials (RCT) of the 4R regimen published in 2018 that included sites in high TB burden settings, as well as earlier phase 1 and phase 2 studies coordinated by the same investigators *(61–64)*. The 4R regimen had already been recommended by WHO for low TB incidence settings by the time the results of the phase 3 trials in children and adults were released in 2018 based on previous evidence. Phase 2 *(63)* and phase 3 *(61,62)* open-label RCTs were conducted in nine countries (Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and Republic of Korea), assigning children (0–17y) and adults (18y and more) with latent tuberculosis infection to receive treatment with 4R or 9H. A documented positive tuberculin skin test (TST) was an enrolment criterion for children; children <5y with negative TST and household exposure to TB were also included. Eligibility in adults was determined by positive TST or IGRA; study criteria for an increased risk of progression to active TB and if their provider recommended treatment with isoniazid. In children, the outcomes were adverse events of Grade 1 to 5 that resulted in the permanent discontinuation of a trial medicine (primary outcome), as well as treatment adherence, adverse event profile, and microbiologically confirmed active TB during 16 months of follow-up after randomization (secondary). In adults, the primary outcome in the phase 2 trial was incidence of grade 3 to 5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active TB within 28 months of randomization. The primary outcome of the adult phase 3 trial was microbiologically confirmed active TB within 28 months after randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active tuberculosis, grade 3 to 5 adverse events, and treatment completion. The outcomes extracted from the trial to address the ones in the PICO were the following (see also the GRADE evidence summary table for PICO 6 in **online Annex 2 of the guidelines**): Incidence of active TB (in all forms) in adults; Incidence of active TB (microbiologically confirmed) in adults; Mortality (all cause) in adults during treatment; Mortality (related to drug) in adults during treatment; Adverse events (Grade 3–5) in adults; Adverse events (Related Grade 3–5) in adults; Treatment completion (ever) in adults; Incidence of active TB (in all forms) in paediatrics; Incidence of active TB (microbiologically confirmed) in paediatrics; Mortality (all cause) in paediatrics during treatment; Mortality (related to drug) in paediatrics during treatment; Adverse events (Grade 3–5) in paediatrics; Adverse events (Related Grade 3–5) in paediatrics; Treatment completion (ever) in paediatrics; Incidence of active TB (microbiologically confirmed) in HIV-positive adults; Incidence of active TB (in all forms) in HIV-positive adults; Adverse events (Grade 3–5) in HIV-positive adults; Adverse events (Related Grade 3–5) in HIV-positive adults. No attempt was made to extract outcomes for emergence of resistance given the incompleteness of data (among the 8 adults with confirmed active tuberculosis in the phase 3 trial, drug-susceptibility test results were not available for four and two had susceptibility to all drugs tested. In the other two, one had resistance to isoniazid detected 8 weeks after starting 9H and one had resistance to rifampicin 2 months after completing 4R. The DST pattern of the putative source case was not available). The GDG decided to downgrade Risk of bias by one level to serious because of the open label design of the trials, possibly leading to performance bias. The risk of detection bias was mitigated by a blinded expert adjudication of active TB and adverse events by a three-member, independent review panel; assessment of treatment completion was based on pill counts at routine follow-up visits. There were 18 per protocol exclusions among those randomized to 9H and 19 per protocol exclusions among those randomized to 4R. These exclusions were due to household contact with isoniazid or rifampicin-resistant TB (proven post-randomization). There were nine individuals randomized to 9H and five individuals randomized to 4R who withdrew consent post-randomization. The GDG noted that Inconsistency could not be judged given that there was only a single trial and replication of findings by other studies would be desirable. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 4R with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TB preventive treatment. Some study sites were low TB incidence settings for which a WHO recommendation for use of 4R already exists. As a result, the certainty

	in the estimates of effect (quality of evidence) was MODERATE for incidence of active TB, mortality, adverse events and treatment completion in both adults and children. However, quality was LOW for all outcomes in HIV-positive adults because of additional downgrading due to imprecision (small numbers of observations in this sub-group which was not stratified at randomization). 61. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. New Eng J Med. 2018 Aug 2;379(5):440–53. 62. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah, J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379:454–463. 63. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2008;149(10):689–697. 64. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med. 2004;170(4):445–449.
Perspective:	The PICO question and GDG discussion were focused on the expected performance of the regimen in high TB burden settings, given that a WHO recommendation for use of 4R in low TB burden settings already exists based upon the evidence reviews conducted for the 2018 update of the WHO LTBI treatment guidelines

Assessment

PROBLEM

IS THE PROBLEM A PRIORITY?

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

DESIRABLE EFFECTS

HOW SUBSTANTIAL ARE THE DESIRABLE ANTICIPATED EFFECTS?

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

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with a regimen of nine months of daily isoniazid	Risk difference with a regimen with four months of daily rifampicin
Incidence of active TB (in all forms) in adults assessed with: RCT evidence follow up: mean 28 months	6859 (1 RCT)[a,b,c,d]	⨁⨁⨁◯ MODERATE[e,f,g]	Rate ratio 0.88 (0.34 to 2.28)[h]	Study population	
				0 per 100[d]	0 fewer per 100 (0 fewer to 0 fewer)[d]
Mortality (all cause) in adults during treatment assessed with: RCT evidence	6485 (2 RCTs)[a,b,i,j]	⨁⨁⨁◯ MODERATE[e,f]	RR 0.11 (0.01 to 2.02)[h,k]	Study population	
				1 per 1,000[i,j]	1 fewer per 1,000 (1 fewer to 1 more)[i]
Adverse events (Grade 3–5) in adults assessed with: RCT evidence	6485 (2 RCTs)[a,b,i,l]	⨁⨁⨁◯ MODERATE[e,f]	RR 0.44 (0.32 to 0.60)[h]	Study population	
				37 per 1,000[i,l]	21 fewer per 1,000 (25 fewer to 15 fewer)[i,l]
Treatment completion (ever) in adults assessed with: RCT evidence	6975 (3 RCTs)[a,m,n]	⨁⨁⨁◯ MODERATE[e,o]	RR 1.25 (1.22 to 1.29)[h]	Study population	
				630 per 1,000[n]	157 more per 1,000 (139 more to 183 more)[n]

Incidence of active TB (in all forms) in paediatrics assessed with: RCT evidence follow up: mean 16 months	829 (1 RCT)[p,q]	⨁⨁⨁◯ MODERATE[e,r,s]	Rate ratio 0.19 (0.01 to 4.02)[h,t]	Study population	
				5 per 1,000	4 fewer per 1,000 (5 fewer to 15 more)
Mortality (all cause) in paediatrics during treatment assessed with: RCT evidence	829 (1 RCT)[p,q]	⨁⨁⨁◯ MODERATE[e,s]	RR 2.89 (0.12 to 70.82)[h,k]	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Adverse events (Grade 3–5) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	⨁⨁⨁◯ MODERATE[e,s]	RR 0.96 (0.06 to 15.37)[h]	Study population	
				2 per 1,000	0 fewer per 1,000 (2 fewer to 35 more)
Adverse events (Related Grade 3–5) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	⨁⨁⨁◯ MODERATE[e,s]	RR 0.96 (0.02 to 48.50)[h,k]	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Treatment completion (ever) in paediatrics assessed with: RCT evidence	829 (1 RCT)[p,q]	⨁⨁⨁◯ MODERATE[e,o]	RR 1.12 (1.05 to 1.20)[h]	Study population	
				771 per 1,000	93 more per 1,000 (39 more to 154 more)
Incidence of active TB (in all forms) in HIV-positive adults assessed with: RCT evidence follow up: mean 28 months	270 (1 RCT)[a,b,c,d,u]	⨁⨁◯◯ LOWe,f,v	Rate ratio 0.48 (0.04 to 5.29)h	Study population	
				14 per 1,000[d,u]	8 fewer per 1,000 (14 fewer to 62 more)[d,u]
Adverse events (Grade 3–5) in HIV-positive adults assessed with: RCT evidence	268 (2 RCTs)[a,b,u,w]	⨁⨁◯◯ LOW[e,f,v]	RR 0.27 (0.06 to 1.23)[h]	Study population	
				58 per 1,000[u,w]	42 fewer per 1,000 (54 fewer to 13 more)[u,w]

[a] Phase 2 *(63)* and Phase 3 *(61)* open-label trials conducted in nine countries, assigning adults with latent tuberculosis infection to receive treatment with a 4-month regimen of daily rifampicin or a 9-month regimen of daily isoniazid. The primary outcome in the phase 2 trial was incidence of grade 3 to 5 adverse events (superiority design), with secondary outcomes of treatment completion and incidence of active tuberculosis within 28 months of randomization. The primary outcome of the phase 3 trial was microbiologically confirmed active tuberculosis within 28 months after randomization (non-inferiority design), with secondary outcomes of clinically diagnosed active tuberculosis, grade 3 to 5 adverse events, and treatment completion. Outcomes of active tuberculosis and adverse events were adjudicated by three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits.

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

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

[d] All active TB events occurred within the phase 3 trial *(61)*.

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

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

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

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

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

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

[h] Unadjusted estimate.

[i] Denominators are representative of the combined safety population of phase 2 *(63)* and phase 3 *(61)* as indicated in supplemental tables S2 and S3 of the phase 3 publication. From the phase 2 trial, 396 patients receiving isoniazid and 393 patients receiving rifampicin formed the safety population; from the phase 3 trial, 2809 patients receiving isoniazid and 2887 patients receiving rifampicin formed the safety population.

[j] All mortality events occurred in the phase 3 trial *(61)*.

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

[l] Among adverse events from the phase 2 trial (*63)*, 10 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 7 were deemed possibly/probably related to study drug; 19 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 16 were deemed possibly/probably related to study drug. Among adverse events from the phase 3 trial *(61)*, 43 patients receiving rifampicin experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 24 were deemed possibly/probably related to study drug; 100 patients receiving isoniazid experienced grade 3–5 adverse events which led to permanent discontinuation of the medication, of which 59 were deemed possibly/probably related to study drug.

[m] Also included is the phase 1 trial *(64)*, a single centre, open-label randomized trial assessing superiority of four months of daily rifampicin to nine-months of daily isoniazid for treatment completion.

[n] Numerator and denominator values are derived from the Phase 1 trial (*64)*, Phase 2 trial *(63)*, and Phase 3 trial *(61)*. Treatment completion was defined as taking at least 80% of prescribed doses (i.e., at least 96 pills of rifampicin or 216 pills of isoniazid). In the phase 1 trial, 44 of 58 individuals randomized to isoniazid and 53 of 58 individuals randomized to rifampicin completed treatment. In the phase 2 trial, 254 of 427 individuals randomized to isoniazid and 328 of 420 individuals randomized to rifampicin completed treatment. In the phase 3 trial, 1890 of 2989 individuals randomized to isoniazid and 2382 of 3023 individuals randomized to rifampicin completed treatment.

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

[p] Open-label, non-inferiority trial conducted in seven countries, assigning children with latent tuberculosis infection to receive treatment with a 4-month regimen of rifampicin or a 9-month regimen of isoniazid for the incidence of grade 3 to 5 adverse events during treatment. Secondary outcomes were the incidence of microbiologically confirmed active tuberculosis within 16 months after randomization and completion of the treatment regimen. Outcomes of active TB and adverse events were adjudicated by two- or three-member, blinded, independent review panels; treatment completion based on pill counts at routine follow-up visits *(61)*.

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

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

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

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

[u] Denominators include HIV-positive patients known at the time of randomization as reported in Supplemental Table S1 of the phase 3 adult trial *(62)*, as well as patients diagnosed post randomization as a result of baseline assessment. This includes 130 patients and 8 patients receiving isoniazid with an HIV-diagnosis at time of randomization and post-randomization, respectively, and 125 patients and 7 patients receiving rifampicin with an HIV-diagnosis at time of randomization and post-randomization, respectively. This resulted in modified intention to treat population sizes of 132 for rifampicin and 138 for isoniazid. Among HIV-positive patients randomized to rifampicin, 2 did not receive a dose of therapy. Thus, the safety population sizes were 130 for rifampicin and 138 for isoniazid.

	[v] Subgroup analysis within randomized trials that involved relatively small numbers of HIV-infected patients when compared to all patients included in the trials. [w] Among patients receiving rifampicin included in the safety population, 6 patients were HIV-positive in the phase 2 trial and 124 patients were HIV-positive in the phase 3 trial. All grade 3–5 adverse events among patients receiving rifampicin occurred in the phase 3 trial. Two patients experienced a grade 3–5 adverse event with rifampicin that resulted in permanent discontinuation of the study drug, only 1 was deemed possibly/probably related to the study drug. Among patients receiving isoniazid included in the safety population, 7 patients were HIV-positive in the phase 2 trial and 131 were HIV-positive in the phase 3 trial. One patient in the phase 2 trial and 7 patients in the phase 3 trial receiving isoniazid experienced a grade 3–5 adverse event resulting in permanent discontinuation of the study medication. The events were deemed possibly/probably related to the study drug for the one patient from the phase 2 trial and for 4 patients from the phase 3 trial.	
UNDESIRABLE EFFECTS		
HOW SUBSTANTIAL ARE THE UNDESIRABLE ANTICIPATED EFFECTS?		
Judgement	Research evidence	Additional considerations
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See tables above	Rifampicin is generally a well-tolerated medicine and the 4R regimen had a good safety profile in the trials. The 4R regimen has been recommended by WHO for use in low TB incidence settings. The GDG agreed that the anticipated undesirable effects would be moderate for the 4R vs. 9H regimen. The likelihood that active TB could be reliably excluded in a high TB burden, low income setting is lower than in a better resourced situation. If the "rule out" algorithm for active TB is inadequate (e.g. limited to symptom screen and without use of chest radiography) then active TB may be inadvertently treated with 4R. There is therefore a greater risk that people with active TB receive rifampicin monotherapy. Other important concerns relate to the effect that rifampicin could have on other medications and substances administered concurrently.

		Interactions with antiretroviral medication in PLHIV (e.g. efavirenz, dolutegravir), with alcohol, with oral or injectable contraceptive medicines in women of childbearing age and with methadone in people on opioid replacement are some of the most likely situations in which significant drug-drug interactions with rifampicin are to be expected. If loose tablets of rifampicin are used more broadly to treat bacterial infections resistance may be propagated. Even though the risk is present there is little evidence that the broad scale up of LTBI treatments, like 4R, generates TB drug resistance.

CERTAINTY OF EVIDENCE		
WHAT IS THE OVERALL CERTAINTY OF THE EVIDENCE OF EFFECTS?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty in the estimates of effect (quality of evidence) was MODERATE for four outcomes considered CRITICAL or IMPORTANT by the GDG in both adults and children: active TB, treatment completion, adverse events of Grade 3 or more, and mortality. However, quality was LOW for all outcomes in HIV-positive adults because of additional downgrading due to imprecision (small numbers of observations in this sub-group and was not stratified at randomization). Insufficient cases were available to assess risk of emergent drug resistance. The reasons why no outcome was considered of HIGH certainty were because of: possible risk of bias from the open label design (even if this was partly mitigated by a blinded expert panel assessment of active TB and adverse events); other risk of bias from a single study by one trial group; possible indirectness given that the comparator is 9H rather than the 6H regimen more widely used in LTBI care.	The GDG concluded that the overall certainty in the evidence was MODERATE. Inconsistency could not be judged given that there was only a single trial; even if the study was multi-country the GDG felt that if the findings can be replicated by other studies – especially in PLHIV - the confidence in the estimates would increase.

VALUES		
IS THERE IMPORTANT UNCERTAINTY ABOUT OR VARIABILITY IN HOW MUCH PEOPLE VALUE THE MAIN OUTCOMES?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The trials did not include an untreated group as a comparator.	The GDG considered that a shorter duration of regimen would be welcome to most people. The GDG considered that there is probably no important uncertainty or variability in how most people value the outcomes but that this may differ between the subgroups, such as PLHIV on ARVs and women on contraceptive medicines. Given that the 4R regimen is already recommended and that rifampicin is a component of other LTBI treatment it was considered that there will be less uncertainty on how best to use this regimen (e.g. dosage, drug-drug interactions) compared to newer ones.
BALANCE OF EFFECTS		
DOES THE BALANCE BETWEEN DESIRABLE AND UNDESIRABLE EFFECTS FAVOR THE INTERVENTION OR THE COMPARISON?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The GDG considered that overall the intervention would be favoured in many settings, regardless of burden/ resources. A shorter duration of LTBI treatment is likely to decrease adverse events and could conceivably reduce the risk of emergence of drug resistance. Concerns were expressed about uncertainty of effect in people in whom rifampicin is contraindicated or in settings where rifampicin-resistance is rife. In such a situation consideration of other LTBI treatment options should be made.

RESOURCES REQUIRED

HOW LARGE ARE THE RESOURCE REQUIREMENTS (COSTS)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	The WHO recommended dosages for the 4R regimen are 10 mg/kg/day in adults and 15 mg/kg/day (range, 10–20 mg) in children. At current Global Drug Facility (GDF) cost, a full course of 4R for an adult >50kg would cost US$24. In contrast in an adult >50kg, 9H costs about US$5, 3HR about US$13 (US$10 in a child (12–15kg)), 3HP costs about US$46, and 1HP about US$70 [as in **August 2019**]. The 4R regimen is likely to require some visits during treatment, which may add costs when compared with shorter rifamycin regimens like 1HP and 3HP.	The GDG considered that resource use will vary depending primarily on the programmatic circumstances, such as the degree of integration with primary health care and adjustments made to accommodate the new regimen. Judging by the drug costs alone as per Global Drug Facility (GDF) prices, to which many low resource countries would be eligible, the 4R regimen in adults would cost about 5 times as much as a 9H regimen, slightly more than a 3HR regimen (which can be delivered with an inexpensive fixed dose combination), and about 2 to 3 times cheaper than the 3 months of weekly rifapentine and isoniazid (3HP) or 1HP regimen respectively. In addition to the GDF drug costs, the GDG examined data collected and analysed by the coordinators of the 4R vs 9H studies (see Tables at left). They estimated health system costs for both regimens by comparing the clinical activities including visits, tests, imaging studies and treatments for people randomized to 4R or 9H. In these trials, 6012 adults and 829 children were included in the mITT populations. Parameters used in the calculations (e.g. higher completion of 4R vs. 9H) reflected observations from the trials. For each study participant, the number of times each activity was performed was multiplied by the unit cost (expressed in Canadian dollars (CAD)) and individual costs were then summed to give a total cost per participant. The source of drug costs was the Global Drug Facility catalogue. Other costs reflect those at the Montreal Chest Institute,

Costs by LTBI regimen at all sites for pediatric patients. *(The source of costs for all tests and activities is Montreal, Quebec – hence for comparison of relative costs)*

	4R		9H		
	Total Costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Ratio of mean costs per MITT patient (4R/9H) 95% CI[1]
N patients (MITT)	422		407		
BASELINE EVALUATION					
Visits ($)	518 63.80	122.90 (0)	50 020.30	122.90 (0)	1.00
Blood tests ($)	9 223.78	21.85 (0.64)	8 933.76	21.95 (0.14)	1.00
Imaging studies ($)	11 072.20	26.23 (2.82)	10 622.70	26.10 (0)	1.00
Procedures	0	-	151.48	0.37 (7.51)	
TB microbiological tests ($)	493.46	1.17 (12.53)	159.26	0.39 (5.25)	3.00
FOLLOW-UP DURING TREATMENT					
Drugs (INH or RIF only – GDF prices) ($)	9 196.22	21.79 (9.21)	3335.31	8.19 (3.83)	2.66
Visits ($)	101 255.21	239.94 (68.93)	191 811.17	471.28 (177.12)	0.51
Blood tests ($)	617.33	1.46 (6.843)	343.84	0.84 (2.09)	1.74
Imaging studies ($)	156.60	0.37 (3.09)	234.90	0.57 (4.63)	0.65
Other microbiological tests ($)	21.950	0.05 (1.06)	26.74	0.07 (1.11)	0.71
COSTS FOR AE CARE					
Visits ($)	0	-	68.25	0.16 (3.38)	
Blood tests ($)	0	-	7.10	0.02 (0.35)	
TOTAL COSTS					
All patients/events ($)	183 900.55	435.78 (76.51)	265 714.81	652.86 (179.94)	0.66 (0.64, 0.69)
Except Adverse events ($)	183 900.55	435.78 (76.51)	265 639.46	652.67 (180.04)	0.66 (0.64, 0.69)
Adverse events only ($)	0	-	75.35	0.18 (3.73)	-

[1] Confidence intervals calculated using the Fieller theorem *(65)*.

Estimated costs by LTBI regimen for all adults in Phase 3, at all sites. *(The source of information for the costs for all tests and clinical activities is Montreal, Quebec – hence relative costs are more informative than absolute costs, or differences in costs)*

	4R		9H		Ratio of mean costs per MITT patient (4R/9H) 95% CI[1]
	Total Costs $ CAD	Mean costs per MITT patient $ CAD (SD)	Total costs $ CAD	Mean costs per MITT patient $ CAD (SD)	
N patients (MITT)	3 023	–	2 989	–	
BASELINE EVALUATION					
Visits ($)	616 692.00	204.0	609 756.00	204.0	1.00
Blood tests ($)	96 867.75	32.04 (19.4)	94 966.93	31.8 (19.2)	1.01
Imaging studies ($)	81 271.00	26.8 (9.7)	80 472.10	26.9 (6.8)	1.00
Microbiological tests ($)	42 142.20	13.9 (55.2)	40 488.72	13.5 (54.5)	1.03
FOLLOW-UP DURING TREATMENT					
Drugs (INH or RIF only) ($)	79 434.94	26.27 (9.98)	17 665.50	5.91 (3.05)	4.4
Visits ($)	757 090.20	250.44 (106.42)	1 234 874.00	413.13 (231.20)	0.61
Blood tests($)	83 476.21	27.61 (23.37)	99 281.90	33.21 (37.09)	0.83
Imaging studies ($)	3 884.35	1.28 (7.24)	4 332.6	1.44 (10.01)	0.89
TB Microbiological tests ($)	722.54	0.23 (6.80)	1 625.41	0.54 (17.0)	0.43
Other microbiological tests ($)	31.53	0.01 (0.40)	71.81	0.02 (0.82)	0.50
Procedures ($)	472.40	0.15 (7.03)	201.74	0.06 (1.75)	2.50
COSTS FOR AE CARE					
Visits ($)	10 731.52	3.549 (29.81)	20 978.5	7.01 (39.19)	0.51
Blood tests ($)	2 700.37	0.89 (9.38)	9 044.14	3.02 (19.63)	0.29
Imaging studies ($)	312.30	0.10 (2.68)	2 776.80	0.92 (9.86)	0.11
Specialist consultations ($)	688.64	0.22 (6.12)	1 396.72	0.47 (11.22)	0.47
Microbiological tests ($)	21.95	0.007 (0.399)	113.04	0.037 (1.32)	0.19
TB microbiological tests ($)	0	–	15.68	0.005 (0.28)	
Procedures ($)	0	–	2 232.75	0.746 (30.95)	
Hospitalization days ($)	8264.40	2.73 (107.73)	35 812.40	11.98 (365.39)	0.23
TOTAL COSTS					
All patients/events ($)	1 784 804.30	590.41 (188.71)	2 256 106.74	754.82 (475.77)	0.78 (0.76, 0.80)
Except Adverse events ($)	1 762 085.12	582.89 (148.28)	2 183 736.89	730.59 (264.28)	0.80 (0.79, 0.81)
Adverse events only ($)	22 719.18	7.51 (128.97)	72 370.03	24.21 (407.63)	0.31 (0.11, 0.86)

[1] Confidence intervals calculated using the Fieller theorem *(65)*.

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

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

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

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES		
WHAT IS THE CERTAINTY OF THE EVIDENCE OF RESOURCE REQUIREMENTS (COSTS)?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	See above	The GDG considered that despite the studies and data on certain resource requirements of the 4R regimen there is low certainty about how widely applicable the information is to the places where the regimen will be used.
COST EFFECTIVENESS		
DOES THE COST-EFFECTIVENESS OF THE INTERVENTION FAVOR THE INTERVENTION OR THE COMPARISON?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		The GDG agreed that a full cost effectiveness analysis with a longer horizon for effects and looking at different populations and settings would be important.
EQUITY		
WHAT WOULD BE THE IMPACT ON HEALTH EQUITY?		
Judgement	Research evidence	Additional considerations
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No included studies	The GDG considered that this regimen is likely to be used without additional resources secured ahead of its introduction and there is therefore a risk its higher price could reduce access to treatment and to other health care services for all people that depend on the same resources. It is therefore possible that equity may be reduced, with certain subgroups benefiting from 4R at the expense of others in whom the regimen is relatively or absolutely contraindicated or in whom ruling out of active TB is more difficult and are therefore more likely to be offered another treatment option.

		Any gains in equity could also change over time if policy in the use of 4R changes. On the other hand, the shorter duration of treatment could mean that more people complete their treatment and therefore protection is more complete and equity is increased for people at risk. The GDG agreed that the introduction of 4R needs to be accompanied by mobilization of appropriate resources from start to avoid shortages in different competing health care needs.
ACCEPTABILITY		
IS THE INTERVENTION ACCEPTABLE TO KEY STAKEHOLDERS?		
Judgement	Research evidence	Additional considerations
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		The GDG considered that programmes may be reluctant to use 4R widely out of concerns of increasing drug resistance in settings where screening for active TB has a poor sensitivity. They may also not want to reintroduce single dose preparations of rifampicin to prevent misuse as a broad-spectrum antibiotic. The higher price of 4R medicines could lower its acceptability compared to alternative LTBI treatments. Conversely, the GDG considered that a shorter regimen may be more acceptable to both the health services and to people at risk without contraindications. The 4R regimen is already recommended by WHO for low incidence settings. Rifampicin is also a component of 3HR, another recommended LTBI regimen in children and adults. The safety profile of rifampicin is very well known and accepted as a medicine for the treatment of active TB.

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

Summary of judgements

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

Type of recommendation

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

Conclusions

RECOMMENDATION

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

JUSTIFICATION

When formulating this recommendation, the GDG considered primarily data from the randomized controlled trials (RCT) of the 4R regimen that included sites in high TB burden settings *(61–64)*. The 4R regimen had already been recommended by WHO for low TB incidence settings by the time the results of the phase 3 trials in children and adults were released in 2018. Phase 2 *(63)* and phase 3 *(61,62)* open-label RCTs have been conducted in nine countries (Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and Republic of Korea), assigning children (0–17y) and adults (18y and more) with latent tuberculosis infection to receive treatment with 4R or 9H. In adults, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was <0.01 cases per 100 person-years (95% confidence interval [CI], −0.14; 0.16); the difference in treatment completion was 15.1% (95% CI, 12.7; 17.4); the difference for Grade 3–5 adverse events was −1.1% (95% CI, −1.9; -0.4). In children, the difference in rate of active TB between 4R and 9H was -0.37 cases per 100 person-years (95% CI, −0.88; 0.14); the difference in treatment completion was 13.4% (95% CI, 7.5; 19.3); the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was −0.0 (95% CI, −0.1; 0.1).

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

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

SUBGROUP CONSIDERATIONS

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

PLHIV: the phase 3 trial evidence reviewed for this recommendation included adults with HIV (4% in each arm of the mITT population) but no children (HIV infection was not an exclusion criterion). The GDG considered however that the recommendation can apply to adults and children with HIV, subject to cautions that apply generally to people taking ARVs with rifampicin. No dose adjustment is required when rifampicin is co-administered with efavirenz. The dose of dolutegravir however needs to be increased to 50 mg twice daily when given together with rifampicin,[1] a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz. Rifampicin can decrease the concentrations of other antiviral drugs: atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir. It should not be used with saquinavir/ritonavir. A key contraindicated drug combination is rifampicin with PIs. A decision on use of 4R in PLHIV on ARVs requires expertise in clinical management of HIV.

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

IMPLEMENTATION CONSIDERATIONS

The GDG considered that the 4R regimen could be an option to offer to people eligible for LTBI treatment regardless of TB burden setting. It should be considered not only as an alternative to 9H, which is how it was investigated in the trials reviewed, but on a broader judgement of the circumstances and other options available for people requiring LTBI treatment. Regimen choice is usually determined based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity or interaction, co-morbidity, availability and preferences. Translation of trial learnings to the programmatic realities will be critical. More advice to help guideline users implement the recommended treatment will be elaborated further in forthcoming WHO operational guidance scheduled for release in 2020.

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

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

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

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

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

[1] Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD). Geneva, World Health Organization; 2018. (https://www.who.int/hiv/pub/arv/DTG-TLD-arv_briefing_2018.pdf)

MONITORING AND EVALUATION

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

As individuals who receive LTBI treatment do not have active disease, their risk for adverse events during treatment must be minimized. Individuals receiving treatment for LTBI should be monitored routinely at monthly visits to health care providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Patients receiving treatment should be advised to contact their health care provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

While most reactions are minor and not serious, attention should be paid in particular to prevent drug-induced hepatotoxicity. Monitoring should focus on liver function. There is no justification to test liver function at baseline in all people to be started on LTBI treatment, but it should be encouraged, where feasible, for individuals with the following risk factors: history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, clinical judgement is required to assess if benefit of TB preventive treatment outweighs the risks; they should be tested routinely at subsequent visits. Appropriate laboratory testing should also be performed for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Trial criteria for when to stop rifampicin - e.g. an increase in transaminases to 5 times the upper limit of normal or to 3 times plus symptoms - will need to be adapted to something more practical under field conditions.

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

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

RESEARCH PRIORITIES

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

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

Population:	In people of all ages at risk of active TB
Intervention:	A regimen with one month of daily rifapentine plus isoniazid ("1HP")
Comparison:	Another regimen (9-months of isoniazid alone [9H] for the study identified and reviewed)
Main outcomes:	Outcomes scored as critical or important by the GDG were: active TB incidence, mortality, adverse events, treatment completion, emergence of drug resistance
Setting:	For this PICO question the GDG considered data from the only known published study of this regimen – **BRIEF-TB/A5279** – a randomized, open-label, phase 3 non-inferiority controlled trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI *(66)*. Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. The primary end-point of this trial was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. LTBI was not confirmed in about 80% of participants. Overall TB incidence observed in the trial was lower than expected. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30); the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority was thus shown; likewise non-inferiority was shown separately for the sub-groups with confirmed LTBI infection, males and females, and for those on or without ARV at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. The outcomes extracted from the trial to address the ones in the PICO were the following (see also the GRADE evidence summary table for PICO 7 in **online Annex 2 of the guidelines**): Incidence of active TB; Incidence of active TB among ART-naive participants at entry; Incidence of active TB among TST or IGRA positive participants at entry; Incidence of bacteriologically confirmed TB; Time to TB diagnosis or death related to TB (with other deaths treated as competing risk); Incidence of active TB or death due to unknown cause; Incidence of active TB or death due to unknown cause; Incidence of active TB or death from any cause; Time to death from any cause; Time to death from tuberculosis; Adverse events (grade 3 or higher of nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy); Serious adverse events; Treatment completion; Treatment completion among ART-naive participants at entry; Emergence of drug resistance to isoniazid among those with confirmed TB and with DST; Emergence of drug resistance to rifampicin among those with confirmed TB and with DST; Emergence of drug resistance to ethambutol among those with confirmed TB and with DST; Emergence of drug resistance to pyrazinamide among those with confirmed TB and with DST

Assessment

PROBLEM

IS THE PROBLEM A PRIORITY?

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

DESIRABLE EFFECTS

HOW SUBSTANTIAL ARE THE DESIRABLE ANTICIPATED EFFECTS?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	<table><tr><th rowspan="2">Outcomes</th><th rowspan="2">No. of participants (studies) Follow up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th>Risk with nine months daily isoniazid</th><th>Risk difference with one month daily rifapentine plus isoniazid</th></tr><tr><td>Incidence of active TB assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years</td><td>2986 (1 RCT)</td><td>⨁⨁◯◯ LOW[a,b,c]</td><td>Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)</td><td>Study population 17 per 1,000</td><td>16 fewer per 1,000 (22 fewer to 11 fewer)</td></tr><tr><td>Incidence of active TB among ART-naive participants at entry assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years</td><td>1486 (1 RCT)</td><td>⨁⨁◯◯ LOW[a,b,c]</td><td>Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)</td><td>Study population 20 per 1,000</td><td>19 fewer per 1,000 (28 fewer to 10 fewer)</td></tr></table>	The GDG members reached agreement that the desirable effects of using 1HP as a LTBI option would be moderate given the notable reduction in treatment time with non-inferior performance. The efficacy of the 1HP regimen shown in the trial suggests that it could be considered as an alternative option for preventive treatment in both low and high resource settings, at least in populations with the same profile as those included in the study, i.e. adolescents and adults with HIV who were not pregnant or breast-feeding. The trial compared 1HP with 9H. However, in many settings where LTBI treatment is used at scale, the normal standard of care would be 6H (i.e. 3 months shorter than 9H).

Incidence of active TB among TST or IGRA positive participants at entry assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	686 (1 RCT)	⨁⨁◯◯ LOW[a,b,c]	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	Study population	
				29 per 1,000	31 fewer per 1,000 (52 fewer to 9 fewer)
Incidence of bacteriologically confirmed TB assessed with: RCT evidence (mITT population); deaths of unknown cause or not related to TB censored follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c,d]	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	Study population	
				-- per --	-- per -- (-- to --)
Time to TB diagnosis or death related to TB, with other deaths treated as competing risk assessed with: RCT evidence (mITT population) follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[c,e]	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	Low	
				17 per 1,000f	2 more per 1,000 (6 fewer to 15 more)
Incidence of active TB or death due to unknown cause assessed with: RCT evidence (mITT population) follow up: mean 3 yearsg	2986 (1 RCT)	⨁⨁◯◯ LOW[c,h]	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	Study population	
				22 per 1,000	23 fewer per 1,000 (30 fewer to 15 fewer)
Incidence of active TB or death due to unknown cause assessed with: RCT evidence (per-protocol population) follow up: mean 3 years	2837 (1 RCT)	⨁⨁◯◯ LOW[c,h]	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	Study population	
				21 per 1,000	21 fewer per 1,000 (27 fewer to 14 fewer)
Incidence of active TB or death from any cause assessed with: RCT evidence (mITT population) follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c]	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	Study population	
				-- per --	-- per -- (-- to --)
Time to death from any cause assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c,h]	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	Low	
				19 per 1,000[f,i]	5 fewer per 1,000 (11 fewer to 6 more)
Time to death from tuberculosis assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,j]	HR 1.00 (0.20 to 4.93)	Study population	
				2 per 1,000	0 fewer per 1,000 (2 fewer to 8 more)

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

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

Adverse events (grade 3 or higher of nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy) assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c]	RR 0.86 (0.58 to 1.27)	Study population	
				35 per 1,000	5 fewer per 1,000 (15 fewer to 9 more)
Serious adverse events assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c]	RR 0.79 (0.59 to 1.04)	Study population	
				72 per 1,000	15 fewer per 1,000 (30 fewer to 3 more)
Treatment completion assessed with: RCT evidence follow up: mean 3 years	2986 (1 RCT)	⨁⨁◯◯ LOW[b,c,k]	RR 1.04 (0.99 to 1.10)	Study population	
				895 per 1,000	36 more per 1,000 (9 fewer to 90 more)
Treatment completion among ART-naive participants at entry assessed with: RCT evidence follow up: mean 3 years	1483 (1 RCT)	⨁⨁◯◯ LOW[b,c,k]	RR 1.05 (0.97 to 1.14)	Study population	
				883 per 1,000	44 more per 1,000 (26 fewer to 124 more)
Emergence of drug resistance to isoniazid among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	26 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,l,m]	RR 1.63 (0.17 to 15.99)	Study population	
				83 per 1,000	52 more per 1,000 (69 fewer to 1,249 more)
Emergence of drug resistance to rifampicin among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	27 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,l,m]	RR 0.81 (0.06 to 11.77)	Study population	
				83 per 1,000	16 fewer per 1,000 (78 fewer to 898 more)
Emergence of drug resistance to ethambutol among those with confirmed TB and with DST	14 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,l,m]	not estimable	Study population	
				143 per 1,000	143 fewer per 1,000 (143 fewer to 143 fewer)
Emergence of drug resistance to pyrazinamide among those with confirmed TB and with DST assessed with: RCT evidence follow up: mean 3 years	12 (1 RCT)	⨁◯◯◯ VERY LOW[b,c,l,m]	not estimable	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

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

Estimated relative risks for different outcomes in TB preventive treatment studies using rifapentine plus isoniazid[1]

				Relative risk					
	Inter-vention	Comparator	N	Active TB	Mortality	Any adverse events	Hepato-toxicity	Drug resistant TB	Completion
PLHIV ≥13 years	1HP	9H	1[2]	-0.13 (-0.52 to 0.27)[3]	0.75 (0.42 to 1.31)	0.79 (0.59 to 1.04)[4]	-	0.81 (0.06 to 11.77)[5]	1.04 (0.99 to 1.10)
Adults with HIV	3HP	6H or 9H	2	0.73 (0.23–2.3)	0.75 (0.44–1.27)	0.63 (0.43–0.92)	0.26 (0.12–0.55)	2.00 (0.26–15.44)	1.25 (1.01–1.55)
	3HP	continuous H	1	1.50 (0.69–3.27)	1.06 (0.47–2.41)	0.20 (0.12–0.32)	0.05 (0.02–0.13)	1.00 (0.09–10.95)	1.59 (1.40–1.80)
Adults without HIV	3HP	9H	1	0.44 (0.18–1.07)	0.75 (0.47–1.19)	0.87 (0.73–1.04)	0.16 (0.10–0.27)	0.47 (0.04–5.18)	1.19 (1.16–1.22)
Children and adolescents	3HP	9H	1	0.13 (0.01–2.54)	0.18 (0.01–3.80)	0.88 (0.32–2.40)	-	-	1.09 (1.03–1.15)

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

1. Information on 3HP studies from the WHO report by Hamada Y, Ford N, Schenkel K, Getahun H. Comparison of 3-month regimen of weekly rifapentine plus isoniazid with daily isoniazid monotherapy for treatment of latent tuberculosis infection: a systematic review. 2017.
2. *(66)*
3. Incidence rate ratio difference / 100 person-years between study and control
4. Serious adverse events
5. Emergence of drug resistance to rifampicin among those with confirmed TB and with DST. The RR for emergence of drug resistance to INH was 1.63 (0.17 to 15.99). Evidence considered of very low quality because apart from restriction to PLHIV, resistance may be non-emergent and coming from infecting strain and small sample of bacteriologically confirmed TB who had drug susceptibility test results

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

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

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

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

		could also be applicable for regimens other than 1HP. Other important future considerations for resources would be about local availability of rifapentine and the development of a low-cost fixed dose combination of HP. In common with other strategies to find people at risk and treat them for LTBI, the implementer will need to put in place appropriate resources not only to supply the medicines but also to find eligible individuals, to test them and to follow them up.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES		
WHAT IS THE CERTAINTY OF THE EVIDENCE OF RESOURCE REQUIREMENTS (COSTS)?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The GDG considered that given the novelty of the 1HP regimen and the lack of data on its programmatic use there remain many uncertainties about resources needed.
COST EFFECTIVENESS		
DOES THE COST-EFFECTIVENESS OF THE INTERVENTION FAVOR THE INTERVENTION OR THE COMPARISON?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		The GDG agreed that a full cost effectiveness analysis with a longer horizon for effects and looking at different populations and settings would be important.

EQUITY		
WHAT WOULD BE THE IMPACT ON HEALTH EQUITY?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No specific studies or evidence	The GDG considered that this regimen is likely to be introduced without additional resources secured ahead and there is therefore a risk that its higher price could reduce access to treatment and to other health care services for all people that depend on the same resources. Given that the eligibility of the regimen still needs to be clarified the effect on equity is likely to vary. The GDG agreed that the introduction of 1HP needs to be accompanied by mobilization of appropriate resources from start to avoid shortages in different competing health care needs. On the other hand, the shorter duration of treatment could mean that more people complete their treatment and therefore when applied at large scale the overall protection of people at risk is strengthened, thus generating more public good and increasing equity.
ACCEPTABILITY		
IS THE INTERVENTION ACCEPTABLE TO KEY STAKEHOLDERS?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies	The GDG considered that a shorter regimen is expected to be more acceptable to people at risk and to health services alike. Rifapentine has now been used globally and knowledge about its safety profile and interactions with other medications is well described and improving. Recent evidence that the dose of dolutegravir may not need to be changed when used with 3HP constitutes an advantage over other rifamycins. However this has

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

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

Summary of judgements

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

Type of recommendation

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

Recommendation

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

JUSTIFICATION

When formulating this recommendation the GDG considered primarily data from the only known published study of this regimen – **BRIEF-TB/A5279** – a randomized, open-label, phase 3 non-inferiority controlled trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone ("9H") in PLHIV who were in areas of high tuberculosis prevalence or who had evidence of LTBI *(66)*. Enrolment was restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (i.e. 1HP arm minus 9H arm) was −0.02 per 100 person-years (95% confidence interval [CI], −0.35; +0.30);

the relative risk (RR) for treatment completion of 1HP over 9H was 1.04 (95% CI, 0.99; 1.10); the RR for Grade 3–5 adverse events was 0.86 (95% CI, 0.58; 1.27); hazard ratio of death from any cause was 0.75 in favour of 1HP (95% CI, 0.42; 1.31); RR for emergence of resistance to isoniazid and rifampicin were, respectively, 1.63 (95% CI, 0.17; 15.99) and 0.81 (95% CI, 0.06; 11.77). Overall non-inferiority as defined by the study protocol was thus shown in the mITT population; likewise non-inferiority was shown separately for the sub-groups with confirmed LTBI infection, males and females, and for those on or without ARV at start of study. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority or noninferiority of 1HP was shown in this stratum. For the discussion resource use was inferred from the costs of medicines on the Global Drug Facility catalogue needed to complete a 1HP treatment. No direct or indirect comparison of the safety and effectiveness of 1HP vs. 3HP was possible although the effects in PLHIV are comparable (see second **Table** above under the section ***Desirable Effects***).

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

SUBGROUP CONSIDERATIONS

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

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

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

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

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

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

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

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

IMPLEMENTATION CONSIDERATIONS

The GDG considered that the 1HP regimen could be an option to offer to people eligible for LTBI treatment regardless of TB burden setting. It should be considered not only as an alternative to 9H, which is how it was investigated in the trial, but on a broader judgement of the circumstances and other options available for people requiring LTBI treatment. Regimen choice is usually determined based on considerations of age, strain (drug susceptible or otherwise), risk of toxicity or interaction, co-morbidity, availability and preferences. Translation of trial learnings to the programmatic realities will be critical. More advice to help guideline users implement the recommended treatment will be elaborated further in forthcoming WHO operational guidance scheduled for release in 2020.

Use of HP in the presence of active TB is highly undesirable as it promotes chronicity and emergence of drug resistance. No effort should be spared to avoid such an eventuality. As for the implementation of any TB preventive treatment a robust algorithm to rule-out active disease is necessary. Rifapentine should not be used to treat other bacterial infections.

There could be differences in long-term effectiveness for LTBI treatment of short duration in PLHIV with severe immunodeficiency or in settings with high TB transmission among PLHIV. Observational studies to assess long-term effectiveness would be important in this respect.

The dosage recommended for 1HP should reflect the ones used in the trial: Isoniazid, 300 mg/day and Rifapentine, 600 mg/day in individuals aged ≥13 years, regardless of weight band.

No data-supported recommendations exist on how to handle interruptions of 1HP, i.e. if missed doses are added at the end and after how many missed doses to start afresh.

If there are contraindications to rifapentine, then an isoniazid regimen of 6 or more months would be the most likely alternative to give. If there is a contraindication for isoniazid (e.g. exposure to confirmed isoniazid monoresistant strain), then probably 4R would be the best option.

MONITORING AND EVALUATION

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

As individuals who receive LTBI treatment do not have active disease, their risk for adverse events during treatment must be minimized. Individuals receiving treatment for LTBI should be monitored routinely at monthly visits to health care providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Patients receiving treatment should be advised to contact their health care provider at any time if they become aware of symptoms such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. If a health care provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately.

Adverse reactions that have been associated with isoniazid (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity) and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity) are those most likely to occur with 1HP. Monitoring should therefore focus on liver function tests, neuropathy and neutropenia. While most reactions are minor and not serious, specific attention should be paid to preventing drug-induced hepatotoxicity. There is no justification to test liver function at baseline in all people to be started on LTBI treatment, but it should be encouraged, where feasible, for individuals with the following risk factors: history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery). For individuals with abnormal baseline test results, clinical judgement is required to assess if benefit of TB preventive treatment outweighs the risks; they should be tested routinely at subsequent visits. Appropriate laboratory testing should also be performed for patients who become symptomatic while on treatment (e.g. liver function tests for those with symptoms of hepatotoxicity). Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, should receive vitamin B6 supplements when taking isoniazid-containing regimens.

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

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

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

RESEARCH PRIORITIES

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

PICO 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.
Option:	3-month weekly rifapentine and isoniazid (3HP).
Comparison:	Isoniazid monotherapy.
Main outcomes:	Incidence of active TB, mortality, adverse events, treatment completion, drug resistance.
Setting:	High-TB incidence countries (estimated TB incidence rate ≥ 100 per 100 000).
Perspective:	Health system and public health.

Background
Treatment of LTBI can reduce the risk for reactivation by 60–90%. WHO currently recommends two approaches for the management of LTBI, based on TB incidence and income. For high-TB incidence countries, WHO recommends isoniazid preventive therapy for 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.

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ● Yes ○ Varies ○ Don't Know	Uptake of LTBI treatment is still suboptimal, with only 38% of 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? ● Yes ○ No ○ Equal ○ Uncertain	We conducted a systematic review with the following subgroup analyses: adults with HIV, adults without HIV, and children and adolescents. Regardless of subgroup, there was no significant difference in the incidence of active TB in participants given 3HP and 6-months' isoniazid (6H) or 9-months' isoniazid (9H). 3HP was associated with higher completion rates (RR, 1.09–1.25) and fewer adverse events (RR, 0.63–0.88) than 6 or 9 months' isoniazid monotherapy in all subgroups. In a comparison of 3HP and continuous isoniazid, the trial showed no significant difference in TB incidence in the intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB or deaths among participants given continuous isoniazid rather than 3HP. 3HP was associated with significantly fewer adverse events than continuous isoniazid (RR 0.20, 95% CI 0.12;0.32).	
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	The overall quality of the evidence was considered high for the comparison between 3HP and 6/9H in adults with HIV, moderate in adults without HIV and in children and adolescents. It was considered moderate for the comparison of 3HP with continuous isoniazid in adults with HIV.	

Values	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ● No important uncertainty or variability	We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf). Data were available from 142 respondents, including 10 reported as HIV-positive. The respondents were asked to rate the importance of each attribute of the LTBI treatment regimen on a five-point scale on which 5 is "very important" and 1 is "not important". More than 90% of the respondents considered the following attributes of preventive treatment to be very important or important: shorter duration, fewer side-effects, fewer visits to the clinic and fewer pills. Fewer respondents rated "less frequent intake" and "no need for DOT" as very important or important (77.3% and 74.4%, respectively). Similarly, while less than 80% of the participants rated "no need for DOT" as very important or important for their children, all the other attributes were rated as very important or important by 90–100%.	
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't Know	No evidence retrieved.	Implementation of 3HP would require more resources, particularly if it is to be given under DOT.
Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ● Varies ○ No included studies	In a cost–effective analysis of 3HP in the USA *(68)*, the cost was assumed to be US$6.00 per 900-mg dose of rifapentine and US$ 0.05 per dose of isoniazid. Over 20 years, 3HP given by DOT would cost the health system US$ 8861 more per TB case prevented and US$ 1879 more per quality-adjusted life year gained than 9H. From the social perspective, 3HP given by DOT was considered cost-saving. The study also found that, if adherence to self-administered 3HP is maintained at levels achieved by DOT, 3HP given by self-administration would cost less than 9H from both a health system and a social perspective.	Varies in different settings depending on cost of the drug and mode of administration (DOT or self-administration).

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

Summary of judgements

	Judgement							Implications
Problem	**No**			**Yes**		**Varies**	**Don't Know**	
Balance of effects	**No**		**Equal**	**Yes**			**Uncertain**	
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**	
Values	**Important uncertainty or 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 ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. *(Conditional recommendation, moderate-quality evidence)*		
Justification	The GDG agreed unanimously that the benefits of 3HP outweigh the harm, given the similar preventive efficacy, safer profile and higher completion rate of 3HP than isoniazid monotherapy. The GDG noted that use of 3HP would require more resources, particularly if 3HP is administered by DOT. One cost-effectiveness study conducted in the USA suggested that 3HP may be more cost-saving than 9-months isoniazid. There was consensus in the GDG that the cost-effectiveness of 3HP depends mainly on the cost of the drug and mode of administration, which would affect the costs to patients and health systems. There was consensus in the GDG that the acceptability of 3HP varies by risk group and setting, due mainly to the mode of administration (self-administration or DOT). The GDG considered that adding 3HP as an alternative to isoniazid would provide more options and hence increase equity.		
Subgroup considerations	The GDG recognized the lack of data on use of 3HP in pregnant women and children < 2 years and stressed the need for data on these populations.		
Implementation considerations	The GDG noted that 3HP can be self-administered. Evidence from an RCT suggests that adherence to self-administered treatment of 3HP is not inferior to DOT. There is little further evidence on use of the 3-month regimen of weekly rifapentine plus isoniazid. The GDG noted that a requirement for DOT could be a significant barrier to the implementation. 3HP should be prescribed with caution to 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.		
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	• 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

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month weekly RPT+isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
2	RCTs	Not serious	Not serious	Not serious[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 *69* and *70*

[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 69

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

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	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 *71*

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 *72*

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 M. tuberculosis 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? ○ No ● Yes ○ Varies ○ 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 *(73)*. Prevention of MDR-TB would reduce the global burden and also address demands from individuals to be protected against development of MDR-TB *(74–77)*.	
Balance of effects	Do the benefits outweigh the harm? ● Yes ○ No ○ Equal ○ Uncertain	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. 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. *(74)* 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.	

Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall quality of the evidence was very low because of very serious risks of bias and imprecision. In the study by Trieu et al. *(75)*, 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.	
Values	Is there important uncertainty about or variability in how much people value the main outcomes? ○ Important uncertainty or variability ○ No important uncertainty or variability ● Minimal uncertainty	We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf). 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.	There is uncertainty about the characteristics of respondents.
Resources required	How large are the resource requirements (costs)? ● Greater resource requirements with the intervention ○ Less resource requirements with the intervention ○ Neither greater nor less ○ Varies ○ Don't know		

Cost effectiveness	Does the cost–effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Favours neither the intervention nor the comparison ○ Favours the intervention ○ Varies ● No included studies		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.
Equity	What would be the impact on health equity? ○ Reduced ● Increased ○ Varies ○ Don't know		
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ● Yes ○ Varies ○ Don't know	Some national or clinical guidelines already recommend preventive treatment for contacts of MDR-TB *(78–80)*.	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.
Feasibility	Is the intervention feasible to implement? ○ No ● Yes ○ Varies ○ Don't know		

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**		**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 ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. *(Conditional recommendation, very low-quality evidence)* *Remarks* The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events. The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV). The drugs should be selected according to the drug susceptibility profile of the source case. Confirmation of infection with LTBI tests is required. This recommendation must not affect on-going placebo-controlled clinical trials of MDR-TB contacts on ethical grounds. The results of such clinical trials are crucial for updating this recommendation. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.		
Justification	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.		
Subgroup considerations			
Implementation considerations	**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 *(81)*. Adverse effects should be monitored according to the WHO framework for monitoring and managing the safety of drugs against active TB *(82)*. The GDG reiterated that strict clinical observation and close monitoring for active TB disease based on sound clinical practice and national guidelines for at least 2 years is required, regardless of the provision of preventive treatment. Consideration should also be given to interactions with antiretroviral, immunosuppressant and other drugs when providing TB preventive treatment. **Informed consent** As the recommendation is based on very low-quality evidence, clients must be given detailed information about the benefits and harms of the preventive treatment and asked for explicit informed consent. In view of the uncertainty about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practice in similar situations.		

	Selection of drug regimen The regimen of preventive treatment of MDR-TB contacts should be based on reliable information on the drug resistance profile of the source case. Later-generation fluoroquinolones (e.g. levofloxacin and moxifloxacin) are considered to be important components of a preventive treatment regimen unless the strain of the source case is resistant to them. Although there has been concern about the use of fluoroquinolones in children because retardation of cartilage development was shown in animals, 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. **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.
Monitoring and evaluation	
Research priorities	• 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 *(74–77)*	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] *(74–76)*	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 *74–77*. Five studies in which fewer than 20 participants completed preventive TB treatment were excluded, as was a study by Kritski *(83)*, 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 *77*

[4] Reference *74*

[5] Reference *76*

[6] Reference *75*

[7] The study by Schaaf et al. *(77)* was excluded as the incidence of MDR-TB was not reported.

References

1. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax. 2013;68(3):247–55.
2. Kasambira TS, Shah M, Adrian PV, Holshouser M, Madhi SA, Chaisson RE, et al. QuantiFERON-TB Gold In-Tube for the detection of Mycobacterium tuberculosis infection in children with household tuberculosis contact. Int J Tuberc Lung Dis. 2011;15(5):628–34.
3. Kenyon TA, Creek T, Laserson K, Makhoa M, Chimidza N, Mwasekaga M, et al. Risk factors for transmission of Mycobacterium tuberculosis from HIV-infected tuberculosis patients, Botswana. Int J Tuberc Lung Dis. 2002;6(10):843–50.
4. Klausner JD, Ryder RW, Baende E, Lelo U, Williame JC, Ngamboli K, et al. Mycobacterium tuberculosis in household contacts of human immunodeficiency virus type 1-seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. J Infect Dis. 1993;168(1):106–11.
5. Bokhari SY, Ahmad A, Shaikh MY, Ahmad I. A study of tuberculosis contacts. J Pak Med Assoc. 1987;37(2):48–52.
6. Biraro IA, Kimuda S, Egesa M, Cose S, Webb EL, Joloba M, et al. The Use of Interferon Gamma Inducible Protein 10 as a Potential Biomarker in the Diagnosis of Latent Tuberculosis Infection in Uganda. PLoS One. 2016;11(1):e0146098.
7. Rutherford ME, Nataprawira M, Yulita I, Apriani L, Maharani W, van Crevel R, et al. QuantiFERON(R)-TB Gold In-Tube assay vs. tuberculin skin test in Indonesian children living with a tuberculosis case. Int J Tuberc Lung Dis. 2012;16(4):496–502.
8. Tornee S, Kaewkungwal J, Fungladda W, Silachamroon U, Akarasewi P, Sunakorn P. Risk factors for tuberculosis infection among household contacts in Bangkok, Thailand. The Southeast Asian journal of tropical medicine and public health. 2004;35(2):375–83.
9. Zelner JL, Murray MB, Becerra MC, Galea J, Lecca L, Calderon R, et al. Bacillus Calmette-Guerin and isoniazid preventive therapy protect contacts of patients with tuberculosis. Am J Respir Crit Care Med. 2014;189(7):853–9.
10. Tuberculosis Research Centre, Indian Council of Medical Research. Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases. Int J Tuberc Lung Dis. 2011;15(6):782–8.
11. Radhakrishna S, Frieden TR, Subramani R, Santha T, Narayanan PR, Indian Council of Medical R. Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study. Int J Tuberc Lung Dis. 2007;11(3):282–8.
12. Narain R, Nair SS, Rao GR, Chandrasekhar P. Distribution of tuberculous infection and disease among households in a rural community. Bull World Health Organ. 1966;34(4):639–54.
13. WHO Tuberculosis Chemotherapy Centre. An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya. Bull World Health Organ. 1961;25(6):831–50.
14. Andrews RH, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan CV, Velu S. Prevalence of tuberculosis among close family contacts of tuberculous patients in South India, and influence of segregation of the patient on early attack rate. Bull World Health Organ. 1960;23:463–510.

15. Loudon RG, Williamson J, Johnson JM. An analysis of 3,485 tuberculosis contacts in the city of Edinburgh during 1954–1955. Am Rev Tuberc. 1958;77(4):623–43.

16. Lewinsohn DA, Zalwango S, Stein CM, Mayanja-Kizza H, Okwera A, Boom WH, et al. Whole blood interferon-gamma responses to mycobacterium tuberculosis antigens in young household contacts of persons with tuberculosis in Uganda. PLoS One. 2008;3(10):e3407.

17. Triasih R, Robertson C, Duke T, Graham SM. Risk of infection and disease with Mycobacterium tuberculosis among children identified through prospective community-based contact screening in Indonesia. Trop Med Int Health. 2015;20(6):737–43.

18. Amanullah F, Ashfaq M, Khowaja S, Parekh A, Salahuddin N, Lotia-Farrukh I, et al. High tuberculosis prevalence in children exposed at home to drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2014;18(5):520–7.

19. Ma N, Zalwango S, Malone LL, Nsereko M, Wampande EM, Thiel BA, et al. Clinical and epidemiological characteristics of individuals resistant to M. tuberculosis infection in a longitudinal TB household contact study in Kampala, Uganda. BMC Infect Dis. 2014;14:352.

20. Rathi SK, Akhtar S, Rahbar MH, Azam SI. Prevalence and risk factors associated with tuberculin skin test positivity among household contacts of smear-positive pulnionary tuberculosis cases in Umerkot, Pakistan. Int J Tuberc Lung Dis. 2002;6(10):851–7.

21. Lienhardt C, Fielding K, Sillah J, Tunkara A, Donkor S, Manneh K, et al. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia. Am J Respir Crit Care Med. 2003;168(4):448–55.

22. Jones-Lopez EC, White LF, Kirenga B, Mumbowa F, Ssebidandi M, Moine S, et al. Cough Aerosol Cultures of Mycobacterium tuberculosis: Insights on TST / IGRA Discordance and Transmission Dynamics. PLoS One. 2015;10(9):e0138358.

23. Whalen CC, Zalwango S, Chiunda A, Malone L, Eisenach K, Joloba M, et al. Secondary attack rate of tuberculosis in urban households in Kampala, Uganda. PLoS One. 2011;6(2):e16137.

24. Kifai EJ, Bakari M. Mantoux skin test reactivity among household contacts of HIV-infected and HIV un-infected patients with sputum smear positive TB in Dar es Salaam, Tanzania. East Afr J Public Health. 2009;6(2):211–8.

25. Nunn P, Mungai M, Nyamwaya J, Gicheha C, Brindle RJ, Dunn DT, et al. The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. Tuber Lung Dis. 1994;75(1):25–32.

26. Espinal MA, Perez EN, Baez J, Henriquez L, Fernandez K, Lopez M, et al. Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: a prospective study. Lancet. 2000;355(9200):275–80.

27. Hesseling AC, Mandalakas AM, Kirchner HL, Chegou NN, Marais BJ, Stanley K, et al. Highly discordant T cell responses in individuals with recent exposure to household tuberculosis. Thorax. 2009;64(10):840–6.

28. Guwatudde D, Nakakeeto M, Jones-Lopez EC, Maganda A, Chiunda A, Mugerwa RD, et al. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. Am J Epidemiol. 2003;158(9):887–98.

29. Lees AW, Allan GW, Smith J, Tyrrell WF. Pulmonary tuberculosis in contacts: a ten year survey. Dis Chest. 1961;40:516–21.

30. Ahmad Khan F, Verkuijl S, Parrish A, Chikwava F, Ntumy R, El-Sadr W, et al. Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. AIDS. 2014;28(10):1463–72.

31. Calnan M. Developing strategies for TB screening among HIV-infected and HIV-uninfected pregnant and postpartum women in Swaziland. 47th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; Liverpool, United Kingdom. 2016.

32. Hanifa Y, Fielding K, Chihota V, Ndlovu N, Karstaedt A, Adonis L, et al. Evaluation of WHO 4-symptom tool to rule out TB: Data from the XPHACTOR Study. Topics in Antiviral Medicine. 2015;23:372–3.

33. Kufa T, Mngomezulu V, Charalambous S, Hanifa Y, Fielding K, Grant AD, et al. Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding, isoniazid preventive therapy, and infection control. J Acquir Immune Defic Syndr. 2012;60(2):e22–8.

34. LaCourse SM, Cranmer LM, Matemo D, Kinuthia J, Richardson BA, John-Stewart G, et al. Tuberculosis Case Finding in HIV-Infected Pregnant Women in Kenya Reveals Poor Performance of Symptom Screening and Rapid Diagnostic Tests. J Acquir Immune Defic Syndr. 2016;71(2):219–27.

35. Nguyen DT, Bang ND, Hung NQ, Beasley RP, Hwang LY, Graviss EA. Yield of chest radiograph in tuberculosis screening for HIV-infected persons at a district-level HIV clinic. Int J Tuberc Lung Dis. 2016;20(2):211–7.

36. Rangaka MX, Wilkinson RJ, Glynn JR, Boulle A, van Cutsem G, Goliath R, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. Clin Infect Dis. 2012;55(12):1698–706.

37. den Boon S, White NW, van Lill SW, Borgdorff MW, Verver S, Lombard CJ, et al. An evaluation of symptom and chest radiographic screening in tuberculosis prevalence surveys. Int J Tuberc Lung Dis. 2006;10(8):876–82.

38. Adetifa IM, Kendall L, Bashorun A, Linda C, Omoleke S, Jeffries D, et al. A tuberculosis nationwide prevalence survey in Gambia, 2012. Bull World Health Organ. 2016;94(6):433–41.

39. Ayles H, Schaap A, Nota A, Sismanidis C, Tembwe R, De Haas P, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. PLoS One. 2009;4(5):e5602.

40. Corbett EL, Zezai A, Cheung YB, Bandason T, Dauya E, Munyati SS, et al. Provider-initiated symptom screening for tuberculosis in Zimbabwe: diagnostic value and the effect of HIV status. Bull World Health Organ. 2010;88(1):13–21.

41. van't Hoog AH, Meme HK, Laserson KF, Agaya JA, Muchiri BG, Githui WA, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. PLoS One. 2012;7(7):e38691.

42. Datta M, Radhamani MP, Sadacharam K, Selvaraj R, Rao DL, Rao RS, et al. Survey for tuberculosis in a tribal population in North Arcot District. Int J Tuberc Lung Dis. 2001;5(3):240–9.

43. Gopi PG, Subramani R, Radhakrishna S, Kolappan C, Sadacharam K, Devi TS, et al. A baseline survey of the prevalence of tuberculosis in a community in south India at the commencement of a DOTS programme. Int J Tuberc Lung Dis. 2003;7(12):1154–62.

44. Kapata N, Chanda-Kapata P, Ngosa W, Metitiri M, Klinkenberg E, Kalisvaart N, et al. The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. PLoS One. 2016;11(1):e0146392.

45. Ministry of Health. Report National TB Prevalence Survey, 2002 Cambodia. Phnom Penh, National Tuberculosis Control Programme, 2005.

46. Ministry of Health. Report on National TB Prevalence Survey 2009-2010. Nay Pyi Taw, Ministry of Health, Department of Health, 2012.

47. Senkoro M, Mfinanga S, Egwaga S, Mtandu R, Kamara DV, Basra D, et al. Prevalence of pulmonary tuberculosis in adult population of Tanzania: a national survey, 2012. Int J Tuberc Lung Dis. 2016;20(8):1014–21.

48. Kebede AH, Alebachew Z, Tsegaye F, Lemma E, Abebe A, Agonafir M, et al. The first population-based national tuberculosis prevalence survey in Ethiopia, 2010–2011. Int J Tuberc Lung Dis. 2014;18(6):635–9.

49. Law I, Sylavanh P, Bounmala S, Nzabintwali F, Paboriboune P, Iem V, et al. The first national tuberculosis prevalence survey of Lao PDR (2010–2011). Trop Med Int Health. 2015;20(9):1146–54.

50. Auguste P, Tsertsvadze A, Pink J, Court R, Seedat F, Gurung T, et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2016;20(38):1–678.

51. Mahomed H, Hawkridge T, Verver S, Abrahams D, Geiter L, Hatherill M, et al. The tuberculin skin test versus QuantiFERON TB Gold(R) in predicting tuberculosis disease in an adolescent cohort study in South Africa. PLoS One. 2011;6(3):e17984.

52. Mathad JS, Bhosale R, Balasubramanian U, Kanade S, Mave V, Suryavanshi N, et al. Quantitative IFN-gamma and IL-2 Response Associated with Latent Tuberculosis Test Discordance in HIV-infected Pregnant Women. Am J Respir Crit Care Med. 2016;193(12):1421–8.

53. McCarthy KM, Scott LE, Gous N, Tellie M, Venter WD, Stevens WS, et al. High incidence of latent tuberculous infection among South African health workers: an urgent call for action. Int J Tuberc Lung Dis. 2015;19(6):647–53.

54. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682–90.

55. Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. PLoS One. 2017;12(1):e0169539.

56. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269–78.

57. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach – Second edition. 2016.

58. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45(6):715–22.

59. Galli L, Lancella L, Tersigni C, Venturini E, Chiappini E, Bergamini BM, et al. Pediatric Tuberculosis in Italian Children: Epidemiological and Clinical Data from the Italian Register of Pediatric Tuberculosis. Int J Mol Sci. 2016;17(6).

60. van Zyl S, Marais BJ, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Adherence to anti-tuberculosis chemoprophylaxis and treatment in children. Int J Tuberc Lung Dis. 2006;10(1):13–8.

61. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. New Eng J Med. 2018 Aug 2;379(5):440–53.

62. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah, J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379:454–463.

63. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2008;149(10):689–697.

64. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med. 2004;170(4):445–449.

65 Fieller EC. The biological standardization of Insulin. Suppl to J R Statist Soc. 1940;7:1–64.

66. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. New Eng J Med. 2019 Mar 14;380(11):1001–11.

67. Stagg HR, Zenner D, Harris RJ, Munoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014;161(6):419–28.

68. Shepardson D, MacKenzie WR. Update on cost-effectiveness of a 12-dose regimen for latent tuberculous infection at new rifapentine prices. Int J Tuberc Lung Dis. 2014;18(6):751.

69. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11–20.

70. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016;30(10):1607–15.

71. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine. 2011;365(23):2155–66.

72. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015;169(3):247–55.

73. WHO. Global TB Report. 2016.

74. Bamrah S, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. Int J Tuberc Lung Dis. 2014;18(8):912–8.

75. Trieu L, Proops DC, Ahuja SD. Moxifloxacin Prophylaxis against MDR TB, New York, New York, USA. Emerg Infect Dis. 2015;21(3):500–3.

76. Garcia-Prats AJ, Zimri K, Mramba Z, Schaaf HS, Hesseling AC. Children exposed to multidrug-resistant tuberculosis at a home-based day care centre: a contact investigation. Int J Tuberc Lung Dis. 2014;18(11):1292–8.

77. Schaaf HS, Garcia-Prats AJ, Hesseling AC, Seddon JA. Managing multidrug-resistant tuberculosis in children: review of recent developments. Curr Opin Infect Dis. 2014;27(3):211–9.

78. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clin Microbiol Infect. 2017;23(3):147–53.

79. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2000;49(Rr-6):1–51.

80. Cain KP, Nelson LJ, Cegielski JP. Global policies and practices for managing persons exposed to multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2010;14(3):269–74.

81. WHO. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. 2014.

82. WHO. Active TB drug-safety monitoring and management (aDSM). Framework for implementation. 2015.

83. Kritski AL, Marques MJ, Rabahi MF, Vieira MA, Werneck-Barroso E, Carvalho CE, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 1996;153(1):331–5.

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