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

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

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

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

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

Assessment

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

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

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

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

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

Adults and adolescents on ART

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

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

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

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

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

Summary of judgements

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

Conclusions

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

Type of recommendation	Symptom screening alone ☐	Symptom screening plus CXR ☒	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	Chest radiography may be offered to PLHIV and on ART and preventive treatment be given to those with no abnormal radiographic findings. *(Conditional recommendation, low-quality evidence)* *Remark: Chest radiography should not be a requirement for initiating preventive treatment.*		
Justification	Overall, the GDG agreed that the screening rule based on four symptoms is very useful for ruling out active TB before providing preventive treatment to PLHIV, regardless of whether they receive ART. It also noted the marginal potential benefits of adding abnormal CXR findings to the four-symptom screening rule. Moreover, increased use of CXR would pick up false-positives to the screening rule, so that more clients would be subjected to investigations for TB and other illnesses. Therefore, the GDG reiterated that CXR adds value only if it does not present a barrier for the provision of preventive treatment for PLHIV. The GDG also noted that symptom screening with or without abnormal CXR findings would be acceptable to individuals and programme managers. Furthermore, the use of CXR could enhance the confidence of health-care providers that active TB has been ruled out and reduce their concern about development of drug resistance. The addition of CXR may incur costs to clients as well as inconvenience, as more clients would have to be investigated for TB and other diseases.		
Subgroup considerations	Although no study was found of the additive role of CXR in testing pregnant women, the GDG noted that pregnant women living with HIV could also benefit, as long as good clinical practices are observed to prevent any significant risk to the fetus. The GDG noted the paucity of data on the usefulness of the screening rule for children living with HIV. The single study showed that the symptom screening rule currently recommended for children with HIV performs well, but no study has been reported on the harm or challenges of the rule, such as resource requirements for implementation. Symptom-based screening is generally accepted by clients and is feasible in resource-constraint settings. Therefore, the GDG decided to make the same strong recommendation.		
Implementation considerations	Addition of abnormal chest radiographic findings to the symptom screening rule would complicate logistics, increasing the cost, workload, infrastructure and availability of qualified staff. The GDG noted that CXR should not be a requirement or a barrier for initiating TPT in PLHIV because of the need for additional resources, in view of the marginal gain in negative predictive value. PLHIV who have any of the four symptoms or abnormal chest radiographic findings may have active TB and should be investigated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test. Other diseases that cause any of the four symptoms should be investigated in accordance with national guidelines and sound clinical practice. PLHIV who present any of the four symptoms but in whom active TB is excluded by investigations may be considered for preventive treatment. The four-symptom screening method is recommended for all PLHIV at every visit to a health facility or contact with a health worker. As combining CXR with symptom screening at every visit could represent a significant burden on the health system as well as on clients, it should be used only to exclude active TB before giving preventive treatment, with due respect for good clinical practice. The role of CXR in regular TB screening and its optimal frequency is uncertain. Local authorities should define its application and frequency on the basis of their local epidemiology, health infrastructure and resource availability. It is essential to ensure the availability of CXR and trained health-care workers (e.g. radiologists) to implement the screening rule.		
Monitoring and evaluation			
Research priorities	• Performance and feasibility of the algorithms proposed in the present guidelines. • In particular, data on the screening rule for children and pregnant women.		

GRADE tables

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

Population: Adults and adolescents with HIV on ART

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

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

From references *31–37*

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

[b] Wide confidence intervals. Downgraded by 1.

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

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

Population: Adults and adolescents with HIV on ART

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

Outcome	No. of studies; no. of patients	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy Quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	Pre-test probability of 5%	Pre-test probability of 10%	
True positives (patients with active TB)	2 studies; 646 patients	Cross-sectional (cohort type)	Not serious	Not serious	Not serious	Serious[a]	None[b]	8 (7 ; 9)	42 (35 ; 46)	85 (70 ; 93)	Moderate
False negatives (patients incorrectly classified as not having active TB)								2 (1 ; 3)	8 (4 ; 15)	15 (7 ; 30)	
True negatives (patients without active TB)	2 studies; 646 patients	Cross-sectional (cohort type)	Not serious	Not serious	Not serious	Not serious	None[b]	295 (260 ; 327)	283 (250 ; 314)	268 (237 ; 297)	High
False positives (patients incorrectly classified as having active TB)								695 (663 ; 730)	667 (636 ; 700)	632 (603 ; 663)	

From references *31 and 36*

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

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

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

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

Assessment

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

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

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

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

Judgement	Research evidence	Additional considerations

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

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

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

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

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

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

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

Summary of judgements

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

Conclusions

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

Type of recommendation	Any CXR abnormality ☐	CXR abnormality suggestive of TB ☐	Any cough ☐	Cough ≥ 2–3 week ☐	Any TB symptom ☐	Any TB symptom plus any CXR abnormality ☒	No recommendation ☐
Strength of recommendation	Strong ☐			Conditional ☒			
Recommendation	The absence of any symptoms and the absence of TB and of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥ 5 years and other at-risk groups before preventive treatment. *(Conditional recommendation, very low-quality evidence)*						
Justification	Overall, the GDG agreed that the potential benefits of screening for active TB with the combination of any CXR abnormality plus any TB symptoms outweighs the harm because of the reliability of this screening rule for excluding active TB before providing preventive treatment. The GDG also noted that symptom screening with or without the addition of abnormal CXR would be acceptable for individuals and programme managers. Furthermore, the use of CXR could enhance the confidence of health care providers that active TB has been ruled out and reduce their concern about development of drug resistance. However, the addition of CXR may incur costs to clients as well as inconvenience, as more clients will be investigated for TB and other diseases.						
Subgroup considerations							
Implementation considerations	Contacts with abnormal CXR findings or TB symptoms must be followed up properly and investigated for TB and other diseases. Investigations should be performed in accordance with national guidelines and sound clinical practice. Contacts in whom active TB is excluded after investigations can be considered for preventive treatment. CXR and trained health care workers (e.g. radiologists) must be available to implement the screening rule. Where CXR is not available, contacts should be screened for any TB symptoms. This would offer the highest sensitivity among the symptom screening rules, and its negative predictive value would remain high in most settings.						
Monitoring and evaluation							
Research priorities	Evidence for the accuracy and feasibility of the recommended screening algorithm under programme conditions. Household models to improve the effectiveness and efficiency of intervention delivery. Studies of cost–effectiveness of screening rules. Strategies to save costs and improve feasibility (e.g. use of mobile CXR).						

GRADE tables

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

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

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

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

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

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

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

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

From references *38–48*

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

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

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

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

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

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

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

Assessment

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

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Balance of effects</td><td>Do the benefits outweigh the harm?
● Yes
○ No
○ Equal
○ Uncertain</td><td>Five relevant studies of IGRA and TST in high TB incidence countries were identified (N = 7769). All were prospective cohort studies of participants who received both TST and IGRA. Two were conducted in India and three in South Africa. The populations studied were PLHIV, pregnant women, adolescents, health-care workers and household contacts. The RRs for test positives and test negatives were estimated for each test and pooled across studies. The pooled RR estimate was 1.49 for TST (95% CI 0.79 ; 2.80, 5 studies, I^2 = 64.4%) and 2.03 (95% CI 1.18 ; 3.50, 5 studies, I^2 = 49.6%) for IGRA. Although the pooled effect estimate for IGRA was slightly higher and the heterogeneity lower than for TST, the 95% CIs around the effect estimates overlapped and were imprecise.

<table><tr><th></th><th colspan="2">TST</th><th colspan="2">IGRA</th></tr><tr><th>Population</th><th>Pooled RR</th><th>I^2 (p value)</th><th>Pooled RR</th><th>I^2 (p value)</th></tr><tr><td>All populations (5 studies)</td><td>1.49 (0.79;2.80)</td><td>64.4% (0.024)</td><td>2.03 (1.18;3.50)</td><td>49.6% (0.094)</td></tr><tr><td>PLHIV (2 studies)</td><td>1.64 (0.24;11.18)</td><td>77.4% (0.035)</td><td>4.07 (0.18;92.72)</td><td>78.7% (0.030)</td></tr></table>
There was little evidence for specific at-risk populations. Two studies were conducted in PLHIV, and the pooled estimates were imprecise.</td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td></td><td></td></tr>
<tr><td>Values</td><td>Is there important uncertainty about or variation in how much people value the main outcomes?
● Important uncertainty or variation
○ No important uncertainty or variation</td><td>No evidence retrieved.</td><td></td></tr>
</table>

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

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

Summary of judgements

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

Conclusions

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

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

Implementation considerations	The GDG noted that the availability and affordability of the tests could determine which LTBI test is used. Other considerations include the structure of the health system, feasibility of implementation and infrastructure requirements. The incremental cost-effectiveness of IGRAs and TSTs appears to be influenced mainly by their accuracy. BCG vaccination plays a decisive role in reducing the specificity of TST, leading the choice towards IGRA-only strategies. The GDG noted, however, that the impact of BCG vaccination on the specificity of TST depends on the strain of vaccine used, the age at which the vaccine is given and the number of doses administered. When BCG is given at birth, as is the case in most parts of the world, it has a variable, limited impact on TST specificity. Therefore, the GDG agreed that a history of BCG vaccination has a limited effect on interpretation of TST results later in life; hence, BCG vaccination should not be a determining factor in selecting a test. IGRAs are more costly and more technically complex to perform than TST. Operational difficulties should be considered in deciding which test to use. For example, IGRA requires a phlebotomy, which can be difficult, particularly in very young children, laboratory infrastructure, technical expertise and expensive equipment; however, only a single visit is required to obtain a result (although patients may have to make a second visit to learn the result). TST is less costly and can be performed in the field, but it requires a cold chain, two health-care visits and training in intradermal injection, reading and interpretation.
Monitoring and evaluation	
Research priorities	New tests with better predictivity for progression from LTBI to active TB disease than current tests. Predictive performance of both tests in various at-risk populations. Cost–effectiveness studies under different conditions of burden and subgroups (e.g. children, PLHIV).

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

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

Systematic review outcome: The predictive utility of the TST vs. the commercial IGRAs for progression to active tuberculosis
Patients/population: Longitudinal studies of adults and children without active TB at baseline not given preventive therapy
Setting: Community cohorts, individuals attending outpatient clinics (e.g. HIV-positive people), individuals participating in RCTs, household contacts; all in high-incidence countries
Index test: TSR (RT23 purified protein derivative or purified protein derivative-S) and/or commercial blood-based IGRAs (QFT-GIT or T.SPOT.-TB)
Importance: Longitudinal studies on the predictive value of a positive IGRA in TB high-incidence countries (≥ 100/100 000) are still emerging. It is important to determine whether IGRA can be used as a replacement for the widely used TST.
Reference standard: All diagnoses of incident active TB (microbiologically confirmed or not)
Studies: Any longitudinal study design (e.g. prospective or retrospective cohort) in TB high-incidence countries, regardless of immunological status (e.g. HIV-infected or not) or BCG status. Average follow-up should be for at least 1 year but can be either active or passive.

No. of studies (no. of individuals)	Design	Quality				Effect		Quality (GRADE)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled)	Absolute effect		
A. Systematic review outcome: Progression to active TB in untreated individuals									
5 (N = 7675 for TST, 7641 for IGRA) *(52–56)*	Prospective cohort	Serious risk of bias (A1) (-1)	Serious inconsistency (TST) I^2 = 64.4%, Serious inconsistency (IGRA) I^2 = 49.6% (A2) (-1)	Not serious (A3)	Serious imprecision (TST) No serious imprecision (IGRA) (A4) (-1)	TST RR = 1.49 (CI: 0.79 ; 2.80) I^2 = 64.4% IGRA RR = 2.03 (CI: 1.18 ; 3.50) I^2 = 49.6%	TST 10 more per 1000 (4 fewer to 37 more) IGRA 15 more per 1000 (3 to 36 more)	Very low	Critical
B. Systematic review outcome (subgroup analysis): Progression to active TB in immunocompromised people (includes HIV and other immunosuppressive conditions)									
2 (N = 725 for TST, 710 for IGRA) *(53,55)*	Prospective cohort of HIV-infected women pre- and post-delivery on ART Prospective cohort of HIV-infected individuals	Serious risk of bias (B1) (-1)	Serious inconsistency (TST) I^2 = 77.4% Serious inconsistency (IGRA) I^2 = 78.7% (B2) (-1)	Serious indirectness (B3) (-1)	Very serious imprecision for both TST and IGRA (B4) (-2)	TST RR = 1.64 (CI: 0.24 ; 11.18) IGRA RR = 4.07 (CI: 0.18 ; 92.72)	TST 39 more per 1000 (46 fewer to 616 more) IGRA 149 more per 1000 (40 fewer to 4438 more)	Very low	Critical

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

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

Notes to the GRADE summary table

Overall quality:
One point was removed from all the studies because none were RCTs. The lowest quality score achievable is 1 out of 4; no minus scores are given.
Quality assessment: Based on the relative effect measure (RR or IRR) for both TST and IGRA. Studies not marked down if estimates for both tests scored high on a specific GRADE quality item.
Other study quality considerations: Newcastle–Ottawa scale quality items were considered when assessing the risk of bias. One point is removed if there is at least one concern.

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

B1: Risk of bias is possible, including selection bias, incorporation bias, ascertainment bias and publication bias. Incorporation bias could not be ruled out for the cohort of antepartum and postpartum women, because relevant information was not available; moreover, there was concern about selection. The reference standards used in the ART cohort study did not include index tests, and the assessors were not blinded to baseline TST results in patient records. Methods for ascertaining TB included microbiological methods, but not all incident TB cases were definitively diagnosed. Publication bias was not formally assessed but is expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
B2: Serious unexplained inconsistency of RR estimates for both TST and IGRA.
B3: This pooled estimate is based on only two studies: one on HIV-infected people on ART with a median CD4+ of approximately 250, and one on HIV-infected antepartum and postpartum women. No direct evidence for treatment of naive patients or HIV-infected patients with high CD4 counts or other sub-populations of HIV-infected individuals (e.g. children).
B4: Very serious imprecision of RR estimates for both TST and IGRA. The 95% CIs are wide and indicate both significant predictive performance and lack of predictivity. The studies had few events.

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

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

E1: Risk of bias is possible, including selection bias, ascertainment bias (inclusion of index tests in methods for ascertaining incident TB) and publication bias. Publication bias was not formally assessed but is expected to be likely. Several large prospective studies are under way or are unpublished, and their results were not included in this analysis; however, additional results are not expected to change the overall conclusions of this review.
E2: Inconsistency not assessed.
E3: This single study comprised adolescents in a high-incidence setting. No direct evidence for other subpopulations of children or adolescents.
E4: No serious imprecision: few events with large sample size.

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

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

Assessment

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

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

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

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

Summary of judgements

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

Conclusions

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

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☒	Conditional ☐	
Recommendation	Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence)*		
Justification	The GDG unanimously agreed that the benefits of 3RH outweigh the harm, given its safer profile, higher completion rate than with isoniazid monotherapy and the availability of child-friendly fixed-dose combinations of rifampicin and isoniazid. The GDG noted that, although the quality of the evidence was low, data on adult populations also support the benefits of 3RH. A systematic review of RCTs on preventive treatment options conducted in 2014 showed that the efficacy and the risk for hepatotoxicity are similar for 3RH and isoniazid monotherapy. The GDG noted that use of 3RH would require fewer resources, given the shorter duration of treatment, which would reduce the number of clinic visits required. It also suggested that the initial cost of use of 3RH would be low, as it is already being used for treatment of active TB. The GDG agreed that cost–effectiveness favours 3RH because of the higher completion rate, safer profile and fewer resources required. The GDG also noted that, although direct evidence for the cost–effectiveness of 3RH in children is limited, the cost–effectiveness of shorter preventive treatment including 3RH is supported by a body of evidence in adult populations. The GDG agreed that there is no important uncertainty or variation in clients' values and preferences. It also agreed that the acceptability of 3RH is high, given its shorter duration and long use by health-care workers for treatment of active TB disease.		
Subgroup considerations			
Implementation considerations	The GDG strongly encouraged use of paediatric fixed-dose combinations of rifampicin and isoniazid for children, as they will increase acceptability and feasibility. It also noted that 3RH should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions; the regimen cannot be co-administered with protease inhibitors or nevirapine. The GDG further emphasized the importance of surveillance systems for rifampicin-resistance TB.		
Monitoring and evaluation			
Research priorities	Further research on reliable methods for excluding active TB among children.		

GRADE table

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

Overall quality: low

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

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

From references *59–61*

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

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

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

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

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

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

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

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

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

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

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

Assessment

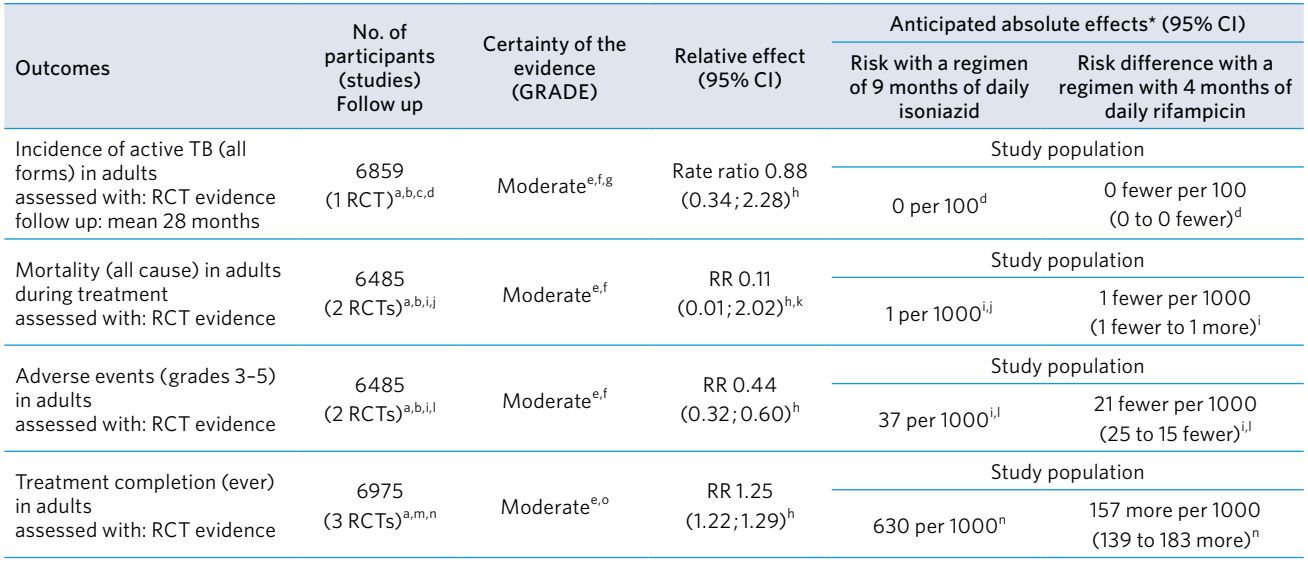
Problem

Is the problem a priority?

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

Desirable effects

How substantial are the desirable anticipated effects?

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

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

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

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

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

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

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

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

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

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

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

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

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

[h] Unadjusted estimate.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Undesirable effects

How substantial are the undesirable anticipated effects?

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

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

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

Resources required

How large are the resource requirements (costs)?

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

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

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

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

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

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

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

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

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

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

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

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

Acceptability

Is the intervention acceptable to key stakeholders?

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

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

Summary of judgements

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

Type of recommendation

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

Conclusions

Recommendation

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

Justification

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

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

Subgroup considerations

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

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

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

Implementation considerations

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

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

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

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

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

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

Monitoring and evaluation

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

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

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

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

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

Research priorities

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

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

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

Assessment

Problem

Is the problem a priority?

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

Desirable effects

How substantial are the desirable anticipated effects?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Certainty of evidence of required resources

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

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

Cost effectiveness

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

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

Equity

What would be the impact on health equity?

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

Acceptability

Is the intervention acceptable to key stakeholders?

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

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

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

Summary of judgements

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

Type of recommendation

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

Recommendation

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

Justification

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

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

Subgroup considerations

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

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

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

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

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

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

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

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

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

Monitoring and evaluation

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

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

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

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

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

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

Research priorities

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

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

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

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

Assessment

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

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

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

Summary of judgements

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

Conclusions

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

Recommendation	In favour of ☒	Against ☐	No recommendation ☐
Strength of recommendation	Strong ☐	Conditional ☒	
Recommendation	Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence. *(Conditional recommendation, moderate-quality evidence)*		
Justification	The GDG agreed unanimously that the benefits of 3HP outweigh the harm, given the similar preventive efficacy, safer profile and higher completion rate of 3HP than isoniazid monotherapy. The GDG noted that use of 3HP would require more resources, particularly if 3HP is administered by DOT. One cost-effectiveness study conducted in the USA suggested that 3HP may be more cost-saving than 9-months isoniazid. There was consensus in the GDG that the cost-effectiveness of 3HP depends mainly on the cost of the drug and mode of administration, which would affect the costs to patients and health systems. There was consensus in the GDG that the acceptability of 3HP varies by risk group and setting, due mainly to the mode of administration (self-administration or DOT). The GDG considered that adding 3HP as an alternative to isoniazid would provide more options and hence increase equity.		
Subgroup considerations	The GDG recognized the lack of data on use of 3HP in pregnant women and children < 2 years and stressed the need for data on these populations.		
Implementation considerations	The GDG noted that 3HP can be self-administered. Evidence from an RCT suggests that adherence to self-administered treatment of 3HP is not inferior to DOT. There is little further evidence on use of the 3-month regimen of weekly rifapentine plus isoniazid. The GDG noted that a requirement for DOT could be a significant barrier to the implementation. 3HP should be prescribed with caution to PLHIV who are on ART because of potential drug–drug interactions. The GDG noted that the 3HP can be administered to patients receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics. Administration of rifapentine with raltegravir was found to be safe and well tolerated. Rifapentine-containing regimens should not be administered with dolutegravir until more information becomes available. The GDG urged further studies on the pharmacokinetics of 3HP with a variety of drugs, particularly ART.		
Monitoring and evaluation	The GDG stressed the importance of recording and reporting on the provision and completion of TPT according to standardized indicators, in order to monitor progress in implementation.		
Research priorities	• Value of self-administration of 3HP. • Studies of pharmacokinetics with a variety of drugs, particularly ART. • Use of 3HP in pregnant women and children < 2 years old.		

GRADE tables

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

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

Overall quality: high

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

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

From references *72* and *73*

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

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

Population: Adults with HIV
Comparison: Continuous isoniazid monotherapy

Overall quality: moderate

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

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

From reference *72*

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

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

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

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

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

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

Overall quality: moderate

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

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

From reference *74*

[a] No study provided a comparison with 6 months of isoniazid. The study included 2.7% HIV-positive participants. Although the trial was conducted in low TB incidence countries, this is unlikely to affect the effect of RPT/isoniazid as compared with isoniazid monotherapy. Downgraded by one level.

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

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

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

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

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

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

Overall quality: moderate

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

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

From reference *75*

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

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

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

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

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

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

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

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

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

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

Assessment

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

Desirable effects

How substantial are the desirable anticipated effects?

Judgement

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

Research evidence

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

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

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

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

Additional considerations

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

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

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

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

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

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement

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

Research evidence

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

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

Additional considerations

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

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

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

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

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

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

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

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

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

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

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

Certainty of evidence of required resources

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

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

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

Equity		
What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Based on a self-administered survey questionnaire among NTP managers of 30 high-burden MDR-TB countries, of whom 18 (60%) responded, overall equity was expected to increase, from the perspective of the managers, for contacts through the avoidance of TB disease incidence. However, 6 NTPs mentioned that certain remote areas may not have an adequate supply of LFX. Additionally, 11 NTPs mentioned increased out-of-pocket spending for contacts, with 2 stating the need for health insurance to cover TPT to ensure equity. Importantly, interviews with contacts themselves in the qualitative acceptability study (36 HHCs from 5 countries) suggested that those with little income, unstable or no employment, little or no social support, will likely NOT be able to accept and complete a 6-month TPT regimen that will require at least monthly check-ups, and maybe some mild side effects, especially at the beginning of treatment that could impact their daily activities and responsibilities (see Annex 5). Also, caregivers for the MDR index patients or other contacts within the household are unlikely to be able to start/accept TPT as well, unless they have access to improved socioeconomic support systems. Hence findings from this qualitative study suggest that equity may be reduced by the introduction of TPT for MDR contacts, unless this is accompanied by improved social and financial support	Key considerations expressed by GDG members when making a judgement of PROBABLY INCREASED for equity were as follows: Some people might benefit more from levofloxacin than others. From a drug perspective there is more equity because we can prevent TB in more people, given the efficacy of the drug. Equity may increase if services are provided to contacts at high risk of drug-resistant TB and who are generally marginalised and who have difficulty to access services. From a model of care perspective, equity is more likely in situations where drug costs are covered by the public health system. Otherwise, the intervention might shift cost to the affected person and lead to out of pocket payments that can reduce equity. So, it is important to think about improving models of care to protect the person needing the drug from incurring cost from the drug and other healthcare system components. In situations where the health system covers the expenditure for levofloxacin, another consideration is about the opportunity cost of investing in levofloxacin as a TPT for MDR-TB. Will the cost of treatment be deducted from another important programmatic component, like TPT for non-MDR-TB or the treatment of people with MDR/RR-TB?

Acceptability		
Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A systematic review of studies published between June 2016 and September 2023 identified five observational quantitative studies that assessed acceptance in starting TPT when offered, willingness to take a hypothetical MDR TPT regimen, and acceptability (ability and willingness to use TPT as directed) of TB prevention treatment with FQ, and a sixth qualitative study conducted in South Africa as a sub-study of the TB CHAMP trial (refer to Annex 5 for studies mentioned in this section). Two studies indicated an 80% acceptance rate among caregivers, for their children to be started on TPT, and among adolescents and adult contacts. Two studies indicated 90% willingness by caregivers and 70% among adults to take TPT for MDR-TB, and one study indicated high levels of acceptability by caregivers administering a novel dispersible child-friendly formulation of LFX to their children. The published qualitative study found an overall high acceptability of LFX among caregivers of children as well but found that there were some pragmatic difficulties around the financial and care burden of providing TPT to their children, especially for caregivers undergoing treatment for TB disease themselves (which was a motivator for accepting treatment but limited capacity to care for children). Greater social support led to greater capability to ensure adherence to treatment for both caregivers and children. A qualitative study conducted among 36 MDR-TB contacts in 5 countries (Georgia, India, Indonesia, South Africa, and Viet Nam) concluded that: TPT for MDR was acceptable and of high social value among participants in all 5 settings. The most acceptable TPT regimen would have a high degree of effectiveness in preventing MDR/RR-TB, no risk of side effects that are permanent or that could interfere with daily activities, few pills and a short duration, low socioeconomic cost, and minimal clinical follow-up visits. A retrospective quantitative sub-study conducted by the V-QUIN investigators examined acceptability among a randomly selected sample of 240 participants in the V-QUIN trial (about equal numbers took placebo, and LFX). They found no major differences in ratings of medication taste, size, frequency of preventative treatment between arms. Of all participants less than 20% rated the duration ideal, and almost one third rated the duration as too long. Acceptability was somewhat worse in those who did NOT complete study drug. Only a minority of participants would take the treatment again or would recommend to others. A prospective quantitative sub-study among all participants in the TB Champ trial examined acceptability on every treatment phase visit and found that the taste of levofloxacin was disliked by children more than placebo, but the children in both arms adapted to the taste over the course of treatment. Caregivers found it more difficult to administer levofloxacin than placebo, but overall, more than 95% of caregivers reported NO difficulty in giving levofloxacin. Overall, the investigators concluded that acceptability was reasonable, but noted an association between poor acceptability and poor adherence. In addition, a semi-structured interview was conducted to evaluate caregiver experience of administering novel child-friendly levofloxacin formulation in 10 child/caregiver dyads on the side of TB-CHAMP. There was a relatively high overall acceptability. One major motivator was the caregivers' own experiences with MDR-TB illness, and treatment. Pragmatic difficulties were expressed around financial and care burden on the household due to TPT. Challenges were exacerbated for caregivers who were on treatment for their own MDR-TB disease, limiting their capacity to care for their children. Caregivers who received greater social support reported better capability for them and their children to adhere to treatment.	Key considerations expressed by GDG members when making a judgement of PROBABLY YES for acceptability were as follows: In the survey of national TB programme managers many stated that they would accept the recommendation only if it is strong. The 6-month duration of treatment may be a challenge although this is the same as the minimum duration of isoniazid that is still one of the most widely used TPT regimens worldwide. Six months has also been the duration of standard treatment for drug-susceptible TB and for the new BPaL(M) regimen for MDR/RR-TB. However, a shorter TPT would be preferred in future. Other factors such as cost, administration issues and the taste of medication were also mentioned as challenges. The high frequency of adverse events in in adults in particular was highlighted. Providing clear information on benefits and risk and a supporting environment to caregivers and beneficiaries is likely to improve acceptability: people's perceptions of the effectiveness and value of TPT are important.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Based on a self-administered survey questionnaire among NTP managers of 30 high-burden MDR-TB countries, of whom 18 (60%) responded, in the case of a strong WHO recommendation, an additional 8 countries (apart from the 6 that were already implementing 6LFX) were ready to implement LFX programme-wide. A conditional recommendation made it less likely for 7 NTPs. All managers anticipated that drug storage, transportation, and distribution was sustainable. However, the need for additional resources (DST, monitoring and follow-up) were raised as concerns/barriers to implementation by 7 of 18 managers.	Key considerations expressed by GDG members when making a judgement of YES for feasibility were as follows: There is already a WHO recommendation for the use of TPT in MDR-TB which has been implemented to some degree despite it being conditional, with levofloxacin being one of the options proposed. Feasibility will depend upon additional resources being available to implement the intervention properly, such as drug-susceptibility testing of the presumed source case and testing for TB infection (in the TB-CHAMP trial a positive tests for infection was not required in most individuals; in the V-QUIN trial adults could participate if TST positive) and chest X-ray (done for participants in both trials). Levofloxacin is widely available as a generic drug in both adult and paediatric formulations.

Summary of judgements

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

Type of recommendation

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

Conclusions

Recommendation

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

Justification

The GDG reached a decision on the strength of the recommendation after a vote in which 11 members out of the 14 present (79%) agreed to a STRONG recommendation, based on MODERATE certainty in the estimate of effects. The main factors that determined this decision were the following:

- the potency of the intervention to achieve its intended effect
- its overall good tolerability, particularly in younger people
- its cost-effectiveness
- the probability that it would increase equity
- a consideration that it would be generally acceptable and feasible

The GDG noted that there is insufficient evidence to make a recommendation on the use of isoniazid as a TPT for MDR/RR-TB. The main considerations leading to this decision were the following:

- the data that were reviewed do not fully address the PICO (ie, data do not compare the effect of isoniazid against levofloxacin or other regimens)
- all studies that were available were observational in nature
- in those offered isoniazid the uptake was low (<20% overall in the individual participant study) and the reasons for not taking it were not known
- there was incomplete information on whether people not taking isoniazid received any other TPT
- the duration of isoniazid use and its dose were not known
- there was no information on whether people who developed TB despite isoniazid had drug-susceptible TB or MDR-TB

Subgroup considerations

Children and adolescents: levofloxacin can be used in children and adolescents, in whom completion and tolerability in the TB CHAMP trial was much better overall. There is no requirement for testing for TB infection before starting levofloxacin in children who are contacts of MDR-TB. Although there has been concern about the use of fluoroquinolones in children because of retardation of cartilage development in juvenile animals exposed to these agents *(77)*, similar effects have not been demonstrated in humans *(78,79)*. While the effects of fluoroquinolones on bone and cartilage in animals have not been observed in humans, available data and infant follow-up times are limited. There remain nonetheless safety concerns associated with prolonged use of fluoroquinolones in humans *(80,81)*.

Pregnancy and breastfeeding: TPT with levofloxacin in pregnancy will require a risk to benefit assessment and an informed choice sought from the pregnant woman on whether or not to take TPT or to defer to the end of pregnancy. The advice should depend on the circumstances (e.g. first trimester vs. later). There is no evidence to support the prolongation of levofloxacin beyond 6 months. Pregnancy increases the risk of progressing from infection to disease and the risk of poor maternal and foetal outcomes should TB disease ensue. MDR-TB in pregnancy is a serious condition and some of the drugs used to treat MDR-TB are or may be toxic to the foetus. Observations from studies in animal exposed to levofloxacin have limited its use in pregnancy. However, one meta-analysis of observational studies with 2800 pregnant women exposed to fluoroquinolones found no differences in birth defects, spontaneous abortion or prematurity compared to unexposed pregnant women *(82)*. Levofloxacin concentrations in breastmilk appear to be far lower than the infant dose and would not be expected to cause adverse effects in breastfed infants *(83)*. Its use should not be suspended during breastfeeding.

Contraindication: levofloxacin should not be given to people who are allergic to fluoroquinolone, who have another contraindication to the class of drugs or who have a potential for a drug-drug interaction. It should be discontinued if the person develops a serious or severe adverse drug reaction to it. In people exposed to a source case with documented resistance to fluoroquinolones another TPT option (see also in Implementation considerations).

HIV infection: levofloxacin can be used regardless of HIV status. In people with HIV exposed to MDR-TB there is no need for a test of infection before starting levofloxacin.

Implementation considerations

The strong recommendation reflects the GDG opinion that the benefits of levofloxacin outweigh the potential harm in most people who are eligible. Health programmes and clinicians should strive to ensure eligibility for its use and maximise the likelihood that treatment is completed as expected. TPT with levofloxacin should also consider factors such as age, risk of toxicity or interaction, co-morbidity, drug susceptibility of the strain of the most likely source case, availability and the individual's preferences.

People receiving TPT should also be supported through access to advice on treatment and management of adverse events at their encounters with the health services. Contacts should be followed up regardless of whether TPT was completed or not. Individuals receiving treatment, clinicians providing treatment and programme managers would prefer shorter to longer regimens. The GDG noted that the 6-month duration of levofloxacin appear long to the patient and caregivers, in comparison to shorter TPT regimens of 4 or 12 week duration that are however only available for prevention of drug-susceptible TB (duration of treatment with delamanid is also for 6 months in the only other ongoing major trial investigating MDR-TB TPT).

Obtaining a positive test for TB infection before starting TPT for MDR-TB is not required in child contacts and people with immunocompromising conditions. In other populations this would be desirable but not mandatory. The unavailability of testing should not be a barrier to provide TPT to individuals who are at risk. Screening of all the household and other close contacts for co-prevalent TB disease will be important.

Levofloxacin is the preferred choice of fluoroquinolone to give as TPT, given that both trials used this agent. While there are no comparable data to support the use of alternatives, moxifloxacin can be used if levofloxacin is not available. Drug-susceptibility testing of the source case strain would be an important additional piece of information, especially in situations where fluoroquinolone resistance is known to be high. If the strain of the presumed source shows resistance to these medicines, other second line drugs can be used as TPT based on the best available information on the drug susceptibility profile of the presumed source. In this case, the certainty of the effectiveness of TPT is much lower than for the use of levofloxacin. Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case isoniazid may be considered effective.

The GDG considered that levofloxacin could be used in any setting, regardless of TB burden, provided that the health infrastructure can ensure the treatment is given correctly without creating inequities, and that TB disease can be excluded reliably before the initiation of treatment. As for other TPT, the GDG noted that treatment can be self-administered and that a requirement for a direct observation could be a significant barrier to implementation. Digital adherence technologies (e.g., electronic medication monitors) may be used to support patients but studies of their use for TPT are sparse.

The model by which care is delivered is important to enhance uptake of the recommendation. If the health system covers the cost of treatment and care then equity could increase. Caregivers should understand why the recommendation is strong in the presence of moderate certainty in the evidence: that high quality evidence from RCTs in different settings showed similar efficacy for a regimen that safely lowers the risk for a life-threatening, infectious condition that is difficult to treat. Engaging stakeholders in the community is important as for other TPT efforts to address the constraints in implementation.

The dosing schedule for LFX in children, adolescents and adults in the guideline have been updated in the operational handbook that accompanies following a discussion with the Technical Advisory Group for dosing of TB medicines in early 2024.

Monitoring and evaluation

Most individuals who receive TPT are healthy and adverse reactions to treatment are likely to influence their likelihood of completing it. Drug-related toxicity should therefore be minimized. Levofloxacin is generally safe and well tolerated but adverse reactions have been reported. Caregivers should be aware of the spectrum of adverse reactions associated with their use so that they can elicit them and take action rapidly. Most reactions are minor and self-limiting, but severe or serious reactions may occur less commonly. Adverse events should be monitored according to the WHO framework for monitoring and managing the safety of medicines against TB disease *(84)*, and pharmacovigilance systems should be strengthened to gather further information about adverse reactions from the long term use of fluoroquinolones. Consideration should also be given to potential interactions with other medicines that the patient may be taking (such as antacids, sucralfate, metal cations, multivitamins, oral antihypoglycaemic agents, warfarin, theophylline, cyclosporine and non-steroidal anti-inflammatory agents). People on levofloxacin should also be advised to contact their healthcare provider at any time if they become aware of symptoms such as inflamed or torn tendons, muscle pain or weakness, joint pain or swelling, difficulty walking, paraesthesiae, burning pain, fatigue, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell. If a healthcare provider cannot be consulted at the onset of such symptoms, the patient should stop treatment immediately. This is one of the critical areas for frontline healthcare workers and students to receive training on.

Individuals on TPT should be monitored routinely at monthly encounters with healthcare providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it. Monitoring the adherence to TPT and ensuring its completion are conducive to clinical benefit. Digital adherence technologies (e.g., electronic medication monitors) have been used to support patients complete curative TB treatment and may have a role in TPT as well.

There is no evidence that the use of fluoroquinolones as TPT has led to the emergence of drug-resistant TB strains in a community. TB disease must be excluded before TPT is initiated, and regular follow-up is required to ensure early identification of people who develop TB disease while receiving TPT. The GDG reiterated that strict clinical observation and close monitoring for TB disease, based on sound clinical practice and national guidelines, is required for at least 1 year after MDR-TB exposure, regardless of whether TPT was taken or not. In people who develop TB after or well into a TPT it would be important to test for emergence of resistance.

There is concern that the expansion of use of fluoroquinolones for TB and other infectious conditions could enhance the emergence of fluoroquinolone-resistant strains and compromise the efficacy of levofloxacin as a TPT. National surveillance systems for anti-TB drug resistance needs to be strengthened in countries scaling up fluroquinolone-containing TB treatment regimens.

Coverage of contact investigation and TPT among contacts and people with HIV are among the top 10 core indicators for monitoring implementation of the End TB Strategy. The use of levofloxacin as TPT for MDR-TB can be integrated in this indicator. National TB and HIV programmes report data yearly to WHO and UNAIDS on progress in TPT scale up in target populations. PMTPT should include monitoring and evaluation systems that are aligned with national patient monitoring and surveillance systems. Standardized indicators should be measured to regularly inform decision-making for programme implementation. Some may require changes to national regulations or health policies (e.g. making TB infection a notifiable condition or mandating a reporting framework), which should be addressed according to the local and national context. It is important to engage the private health sector and to ensure proper recording and reporting from both the private and public sectors. Electronic applications for mobile phones and other devices can be used to guide national programmes on critical data to collect along the TB preventive care pathway, as an accessory to monitoring and evaluation (e.g. PREVENT TB app, https://www.who.int/activities/preventing-tb#app). Such application could also be helpful to collect information about the occurrence of TB disease in people who have received TPT with levofloxacin. This can be done by asking patients registered for TB treatment about any history of starting or completing TPT or the cross linkage of registers (e.g. registers of people given TPT compared with TB treatment or mortality registers).

(More detail is provided in the updated operational handbook that WHO is releasing with these guidelines)

Research priorities
The evidence reviewed ahead of the current update exposed research gaps in the area of TPT for MDR/RR-TB. Continued research remains important for several aspects of the TPT. Information to fill these gaps needs to be collected in part through special trials and in part as implementation research under programmatic conditions.
The new, strong recommendation by WHO for levofloxacin as TPT for MDR/RR-TB should not signal no further need to study this subject, or create ethical impediments for ongoing or future trials exploring other regimens as TPT.
It will be critical to develop TPT regimens for MDR-TB that are shorter than 6 months and with good safety profile in childhood, pregnancy and in the presence of co-morbidities or risk of drug-drug interactions. Pregnancy should not be an absolute exclusion criterion in such studies.
The long-term efficacy of TPT regimens for MDR-TB would be important to understand especially in settings with high risk of MDR-TB re-exposure. Monitoring the efficacy of fluoroquinolones and other TPT in areas with high levels of resistance in TB strains to the medications used as TPT will be useful. Exploring regimens that remain effective in the presence of fluoroquinolone-resistant TB strains will be important in areas of high fluoroquinolone resistance.
Programme-based surveillance and studies of special design are needed to monitor for the emergence of clinically-relevant resistance to fluoroquinolones in TB and other bacterial strains and to other the medicines used at large scale for TPT.
The collection of programmatic data on adverse events and maternal and pregnancy outcomes, inclusive of post-natal follow-up of the child, could supplement current knowledge about the safety of levofloxacin TPT when used in pregnancy and breast-feeding.
Studies about the effectiveness of context-specific interventions to enhance adherence and completion of treatment, such as self-administration with and without the use of digital adherence technologies, will be helpful. Implementation research on context-specific barriers and facilitators is needed for TPT to MDR-TB, to explore dimensions for which evidence is often sparse, such as acceptability, feasibility, equity and resource use.
Continued epidemiological research is needed to determine the burden of TB infection in specific geographical settings and risk groups, and risk of progression, as a basis for nationally and locally tailored interventions, including integrated community-based approaches.
Research is also needed on service delivery models for TPT, to lower costs, enhance equity and to optimize the follow-up of people exposed to MDR-TB, whether or not they received fluoroquinolones, in terms of duration, monitoring approaches, and frequency of visits. Future evidence could guide better how to optimise contact tracing strategies in households as well as how to deliver public health interventions for common modifiable risk of affected people, such as use of tobacco, drugs and alcohol.

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Annex 5. Summary of unpublished studies (PICO 10)

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

Tuberculosis Child Multidrug-Resistant Preventive Therapy Trial (TB CHAMP): Efficacy and safety of levofloxacin preventive treatment in child and adolescent HHCs of multidrug-resistant tuberculosis (MDR-TB). Author: Anneke Hesseling[7]

V-QUIN MDR-TB prevention study: Levofloxacin versus placebo for the treatment of tuberculosis infection among contacts of patients with MDR-TB. Author: Greg Fox[8]

Methods

TB CHAMP: A phase III cluster double-blind group randomized placebo-controlled trial to assess the efficacy and safety of a 6-month regimen of daily levofloxacin (6Lfx) as TB preventive treatment (TPT) in child contacts of patients with MDR-TB. The trial protocol was registered at ISRCTN registry (ISRCTN92634082; https://doi.org/10.1186/ISRCTN92634082)

V-QUIN: Double-blind parallel group randomized controlled trial to compare a 6-month regimen of daily levofloxacin (6Lfx) with placebo for the treatment of TBI. The objective was to determine the efficacy of levofloxacin (Lfx) in preventing the development of bacteriologically confirmed TB. The trial was registered prospectively with the Australian and New Zealand Clinical Trials Registry (ACTRN 12616000215426; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817)

Objectives

TB CHAMP

Primary objective: To assess whether Lfx given daily for 24 weeks (15–20 mg/kg) is effective in preventing TB in child HHCs (HHC) of adults with MDR-TB

Secondary objectives

1. Does Lfx have acceptable toxicity and tolerability in children?
2. Is adherence similar in the study arms?
3. Is Lfx cost-effective and acceptable to prevent MDR-TB in child HHC?
4. Are there differences in Lfx resistance between study arms for children who develop incident TB?

V-QUIN

Primary objective: To evaluate the effectiveness of Lfx given for 6 months rather than placebo in prevention of TB disease among HHC of patients with MDR/RR-TB who have TB infection.

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[7] Stellenbosch University, Cape Town, South Africa

[8] University of Sydney, Sydney, Australia

Secondary objectives: evaluation of:

1. incidence of grade 3–4 adverse events
2. mortality
3. adherence to treatment (completion of > 80% of doses in < 270 days)
4. cost-effectiveness
5. acquired resistance to Lfx

Intervention

TB CHAMP: comparison of 24 weeks of daily Lfx (15–20mg/kg, maximum 750 mg) to 24 weeks of daily placebo.

V-QUIN: 180 days of self-administered oral Lfx, or an indistinguishable placebo, once per day. Tablets were distributed every 4 weeks, and a pill count performed at each visit. The daily dosing range was 10–15 mg/kg for adults, and 15–20 mg/kg for children, with a maximum dose of 750 mg.

Population eligibility

TB CHAMP

The study was completed in urban and rural settings of five provinces in South Africa, a high-incidence country for TB, TB/HIV and MDR/RR-TB. Children were considered eligible for enrolment if they fulfilled all the inclusion criteria and none of the exclusion criteria, as defined below.

Criteria for inclusion of a child or adolescent participant

- child or adolescent < 18 years who is a HHC of an adult MDR-TB index case (as stated under adult MDR-TB eligibility criteria) (up to version 2.0 protocol, only children aged < 5 years were eligible)
- primary residence in the household of the adult MDR-TB index patient or any contact resulting in significant exposure of the child
- consent from the parent or legal guardian for HIV testing
- consent from the parent or legal guardian for enrolment
- assent obtained from any child or adolescent ≥ 7 years
- if > 5 years and < 18 years of age, the child or adolescent must have a positive IGRA (Quantiferon-Gold Plus, Qiagen) test before enrolment, unless HIV positive. Children < 5 years eligible regardless of IGRA status. All HIV-positive children < 18 years of age are eligible regardless of IGRA test status.

Criteria for exclusion of a child or adolescent participant

- TB disease at enrolment
- currently on INH or a fluoroquinoline (e.g. Lfx, moxifloxacin, ofloxacin or ciprofloxacin) for ≥ 14 days. TPT may be interrupted provided that the child or adolescent participant is recruited into the study as soon as possible.
- treated for TB in the previous 12 months
- known concurrent exposure to an INH-susceptible (including rifampicin [RIF] mono-resistant) index case
- weight < 3.0 kg
- positive pregnancy test at enrolment (For women who become pregnant on study, continuation on study treatment is allowed.)
- ≤ 6 months post-partum

Inclusion criteria for adult index patients

- age ≥ 18 years

- bacteriologically confirmed pulmonary TB diagnosed from a sputum sample, treatment for MDR-TB started within the preceding 6 months
- genotypic or phenotypic resistance to INH and rifampin (RIF). If only tested by Xpert MTB/RIF or MTB/RIF Ultra or other approved molecular tests e.g. line probe assay, the index case can be included if RIF-resistant, without other confirmed DST; i.e. confirmation of both RIF and INH resistance not required.
- written informed consent from the index case (or a close relative if the index case is deceased prior to the completion of screening)
- at least 1 HHC below the age of 18 years reported to have been residing in the same household as the adult index case in the previous 6 months

Exclusion criteria for adult index patients

- MDR-TB with confirmation of genotypic or phenotypic resistance to fluoroquinolones (FQs) (version 3.0 protocol)

V-QUIN

The study was conducted in Viet Nam, which is among the high-incidence countries for TB and MDR/RR-TB. Participants were recruited in urban and rural settings in 10 provinces. The study sites delivered standard programmatic management of drug-resistant TB within the National Tuberculosis Programme (NTP).

Inclusion criteria for randomization

- all ages (participants < 15 years were enrolled only during the final 6 months of recruitment in conformity with the requirements of the local institutional review board)
- either:
  (1) tuberculin skin test (TST) positive, defined as either (a) ≥ 10 mm first reading; (b) new TST conversion on the second reading (≥ 10 mm at second reading and an increase of ≥ 6 mm at the second reading over the first reading, OR
  (2) any TST size if known HIV positive or severely malnourished (body mass index < 16 kg/m^2).

Exclusion criteria

- current TB disease
- known to be pregnant
- unable to take oral medication
- body weight < 3 kg
- unwilling or unable to participate in follow-up
- currently breastfeeding
- known allergy to FQ antibiotics or history of severe tendinopathy related to FQs
- currently taking another medication reported to increase the cardiac QTc interval
- documented previous treatment for MDR-TB
- documented treatment with antibiotics that are active against MDR-TB in the previous months
- prior severe blistering reaction to tuberculin
- end-stage liver failure (class Child-Pugh C)
- dialysis-dependent chronic kidney disease
- a baseline liver function test, aspartate or alanine aminotransferase over three times the upper limit of normal
- kidney tests show end-stage kidney disease (estimated glomerular filtration rate < 20 mL/min)
- platelet count < 50 × 10^9 cells/L
- baseline electrocardiogram shows a QT segment > 450 ms (adults)

Randomization and trial procedure

TB CHAMP: All eligible children in a household were treated with the same drug (either all Lfx or all placebo). Households were randomized (allocated by chance) to be in the Lfx or the placebo group. Allocation conducted by computer, and households had an equal chance of being in either group. In this "double blind" study, neither the children (or their family) nor the researchers knew whether the tablets each child took were Lfx or placebo.

A CXR (anteroposterior and lateral images) was completed at baseline and, if any evidence of TB on the CXR or if the child had any symptoms or signs suggestive of TB, they underwent sampling for mycobacterial evaluation. IGRA and HIV testing were done in all children at baseline, and the result was required before enrolment of children aged 5–17 years. A pregnancy test was performed at baseline for all female participants who had begun menstruation. A full blood count, alanine transaminase and bilirubin were collected at baseline in all children. Children were followed at 4, 8, 12, 16, 24, 48 and 72 weeks and at additional unscheduled visits as clinically indicated. At each visit, children were assessed clinically for symptoms and signs of TB, new exposure to TB and for evidence of any adverse events due to the medication. Adherence to medication was quantified by pill returns and counts, treatment diaries and questionnaires. Weight and height were measured at each visit, all concomitant medications documented, and any outpatient or inpatient health-care visits were recorded. The dose of medication was adjusted monthly as necessary. A CXR (AP and lateral) was done at baseline and at 12 and 48 weeks and at any time of clinical concern. Two respiratory samples were collected for mycobacterial evaluation if the child had any symptoms or signs suggestive of TB or if they had an abnormal CXR. Sampling for presumed pulmonary TB consisted of induced sputum or gastric aspiration in children < 5 years, while children aged ≥ 5 years were encouraged to produce an expectorated sputum sample. Samples for presumed extrapulmonary TB were taken according to the site of disease. All samples were examined by smear microscopy, Xpert MTB/RIF Ultra and mycobacterial culture. Drug susceptibility (first- and second-line drugs) was tested in all mycobacterial isolates by genotypic and phenotypic methods.

V-QUIN: Participants were assigned to parallel groups in a 1:1 ratio in a permuted block design with varying block size, stratified by province. The allocation sequence was concealed before randomization. Within a household, participants were placed on the same regimen if enrolled within 90 days of one another to avoid a contamination effect.

During the 6-month treatment period, participants attended a clinic monthly to assess toxicity and support adherence. Patients were also telephoned between scheduled visits, every 2 weeks. After treatment, participants attended follow-up sessions for assessment of incident TB with a symptom screen and CXR at 6, 12, 18, 24 and 30 months. In addition, patients were assessed by telephone interviews for symptoms every 3 months during the follow-up. Throughout follow-up, participants with symptoms consistent with TB or CXR abnormalities were asked to produce three sputum samples for Xpert MTB/RIF and liquid culture. After the 30-month follow-up period (up to 134 weeks), participants were asked to produce a single sputum sample for Xpert MTB/RIF testing. Those diagnosed with TB disease were treated with a standard first- or second-line regimen according to national guidelines and the drug susceptibility profile – if available.

Outcome ascertainment

TB CHAMP: The primary end-point for efficacy was incident TB disease (bacteriologically confirmed or clinically diagnosed) or death from TB at the 48-week study visit after randomization, with a 6-week window allowed, i.e. through week 54. The prespecified main secondary end-point for safety was adverse events (AEs) grade ≥ 3 assessed by the site investigator as at least possibly associated with the study treatment. Other secondary end-points included:

- TB disease by 72 weeks
- all-cause mortality

- any AEs grade ≥ 3 from starting study treatment up to 30 days after the last study drug dose
- serious AEs up to 30 days after the last study drug dose
- discontinuation of study treatment due to AE(s)
- selected pre-defined AEs, from starting treatment up to 30 days after the last study drug dose unless stated otherwise (arthritis, arthralgia, tendinopathy during overall study follow-up, peripheral neuropathy, central nervous system effects, severe rash/cutaneous reaction and drug related fever)
- treatment adherence.

Incident TB and cause of death were adjudicated by an independent end-point review committee who were unaware of the randomized treatment allocation, according to all available clinical, radiological, microbiological and molecular data according to standard international consensus case definitions.

V-QUIN: Outcomes were reported for each participant. The primary study end-point was bacteriologically confirmed TB, defined as a positive identification of *M. tuberculosis* by culture or a molecular WHO-recommended rapid diagnostic in a close contact with clinical and/or radiological evidence of TB disease. The primary outcome was assigned by an expert clinical panel that was blinded to group allocation.

Secondary end-points included all forms of TB (bacteriologically confirmed or clinically probable), completion of therapy, treatment discontinuation due to an adverse event, grade 3 or 4 adverse events, death from any cause except violence, accident or acquired resistance to FQs in comparison with the index isolate. Completion of treatment was defined as having taken at least 80% of doses within 270 days after starting therapy. Secondary safety outcomes were assigned by an expert clinical panel that was blinded to group allocation.

Statistical methods

TB CHAMP

Sample size

In the original sample size calculations, a 50% reduction in TB disease incidence was assumed by 48 weeks (i.e. 50% efficacy of Lfx), from 7% in the control group to 3.5% in the Lfx group. The originally calculated sample size was 1556 participants, which would provide 80% power for the study at a 5% two-sided significance level, assuming an average of two participants enrolled per household; the household intra-class correlation was 0.10, with 10% loss to follow-up. In May 2019, after discussion with the Trial Steering Committee and the Independent Data Monitoring Committee, the target sample size was reduced to 1009 according to an assumed efficacy of 60% for Lfx (with other assumptions remaining unchanged). This assumption was considered to be in line with the results of the meta-analysis by Marks et al. (2017, doi:10.1093/cid/cix208).

Statistical analyses

- primary efficacy analysis included all randomized participants except for any late screening failures due to TB at baseline (mITT population);
- pre-defined ± 6-week window allowed for study visit at 48 weeks, with follow-up time censored at 54 weeks;
- Cox regression used to estimate hazard ratio of time to TB end-point with Lfx compared with placebo, accounting for household clustering and adjusting for site and age group;
- safety analyses included all randomized participants who had received at least one dose of study drug and comparison of time to first event between treatment arms; and
- IPD and Bayesian analysis: TB-CHAMP and V-QUIN

V-QUIN

Sample size

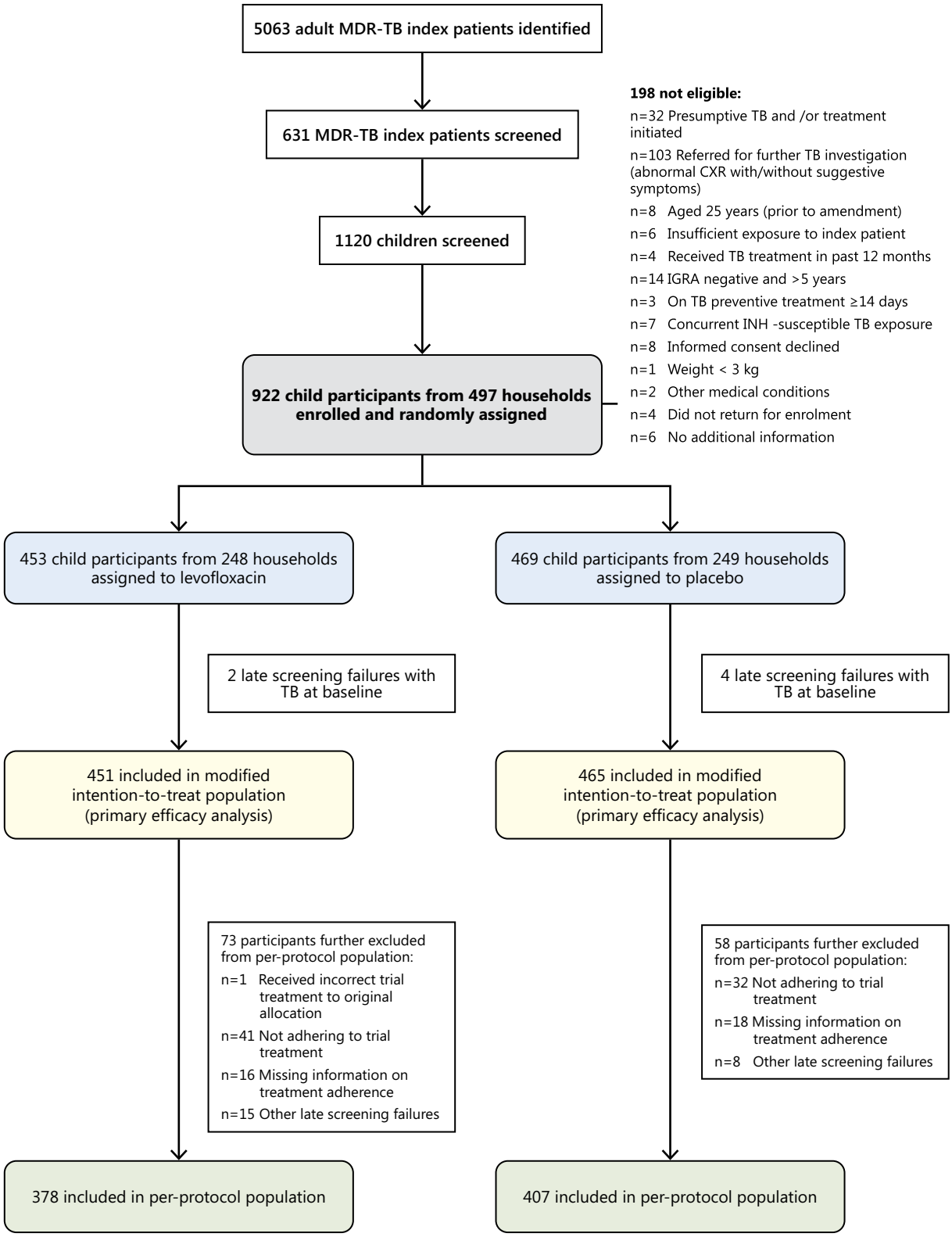
The risk of incident TB in the placebo group was expected to be 3% during the follow-up period, with an expected reduction in incident TB with Lfx by 70% in the treatment group, based on estimates of isoniazid efficacy in DS-TB. The sample size was increased to allow for 17% FQ resistance among patients with RR/MDR-TB in Viet Nam, a 10% drop-out rate and a design effect of 1.04 at district level and 1.07 at household level. To determine superiority, the required sample size was 1003 per arm on the basis of a two-sided alpha level of 0.05 and a power of 80%, allowing for clustering at district and household levels.

Statistical analyses

- The analysis was conducted according to a plan. Group assignment was blinded until analyses were complete. The primary analysis included the intention-to-treat (ITT) population. ITT analyses were also performed on the secondary (composite) outcomes of bacteriologically confirmed or clinically probable TB and all-cause mortality. The per-protocol population included all randomized participants who completed at least 80% of their assigned treatment. The mITT population excluded contacts of patients with RIF-susceptible TB and participants who did not start therapy.
- An interim safety analysis was performed to assess the rate of grade 3 and 4 adverse events after 600 contacts had completed 6 months of therapy. A pre-specified secondary Bayesian analysis was conducted to evaluate the incidence of confirmed or clinically probable TB at 54 weeks.
- The incidence rate ratios and 95% confidence intervals (95% CIs) were estimated in a marginal Poisson regression model fitted via generalized estimating equations.
- A complete case analysis was performed for the primary and secondary analyses.

Fig. A5.1. CONSORT diagram

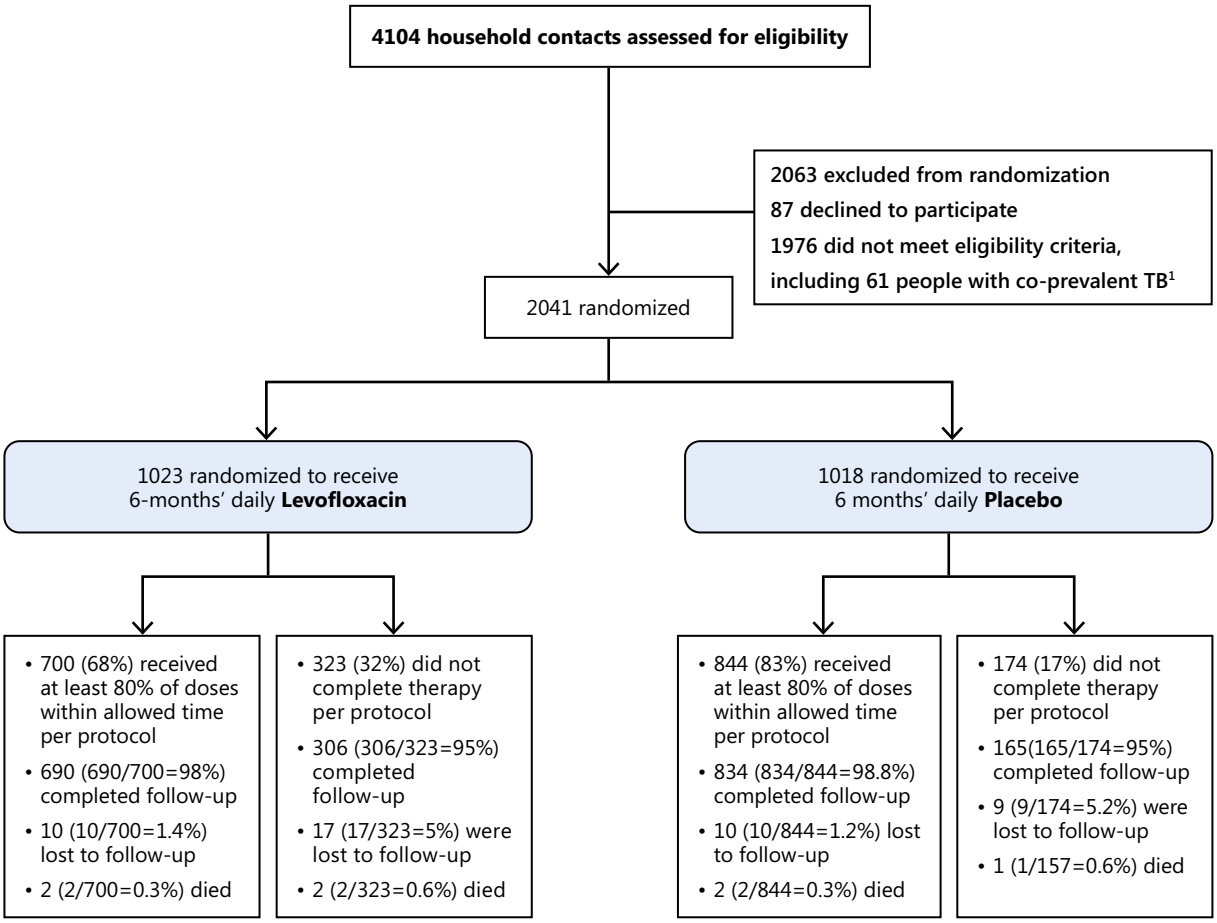
TB CHAMP: Overview of enrolment, randomization and analysis of multi-drug-resistant tuberculosis child HHCs



MDR, multidrug-resistant; TB, tuberculosis; CXR, chest x-ray; IGRA, interferon-γ release assay; INH, isoniazid

Of the 5063 adult index patients identified, 631 were screened. Index patients were ineligible for screening because: the study team was unable to establish contact with the index patient, the index patient had died or moved, the index patient was < 18 years of age, the index patient had RIF-mono-resistant TB, had been on treatment for more than 6 months, had non-pulmonary TB, or no children < 5 years were reported to be living in the household during the past 6 months.

Fig. A5.2. V-QUIN: recruitment of HHCs



[1] *Co-prevalent TB 4 people with bacteriologically confirmed and 17 people with clinically diagnosed TB*

Results

TB CHAMP

Table A5.1. Baseline characteristics of randomized child participants (N=922)

Participants randomized (N)		Levofloxacin 453 (100%)	Placebo 469 (100%)	Overall 922 (100%)
Female		240 (53%)	228 (49%)	468 (51%)
Age (years)	Median (IQR) years	3.0 (1.4, 4.3)	2.6 (1.3–4.1)	2.8 (1.3–4.2)
	<1	85 (19%)	83 (18%)	168 (18%)
	1–<3	140 (31%)	175 (37%)	315 (34%)
	3–<5	180 (40%)	176 (38%)	356 (39%)
	5–<10	18 (4%)	17 (4%)	35 (4%)
	10–<15	20 (4%)	13 (3%)	33 (4%)
	15–<18	10 (2%)	5 (1%)	15 (2%)
Black race		362 (80%)	381 (81%)	743 (81%)
BCG vaccinated		423 (94%)	442 (95%)	865 (94%)
HIV-positive		10 (2%)	9 (2%)	19 (2%)
HIV-exposed uninfected		153 (34%)	160 (34%)	313 (34%)
Currently on TB preventive treatment		9 (2%)	6 (1%)	15 (2%)
Weight-for-age Z score, median (IQR)		-0.4 (-1.2–0.3)	-0.4 (-1.2–0.4)	-0.4 (-1.2–0.3)

Children and adolescents aged 5–17 years were required to be IGRA-positive or living with HIV to be eligible

BCG, bacille Calmette-Guérin; IQR, interquartile range

Table A5.2. Primary efficacy analysis – mITT population

mITT population	Levofloxacin	Placebo	Total
All participants	451	465	916
Participants with ethics review committee adjudicated TB endpoint during overall study follow-up	7 (1.6%)	14 (3.0%)	21
Confirmed TB	3	7	10
Unconfirmed TB	4	7	11
Primary efficacy analysis			
Participants with TB end-point by 48 weeks[a]	5 (1.1%)	12 (2.6%)	17
Confirmed TB	3	7	10
Unconfirmed TB	2	5	7
Hazard ratio (95% CI), Levofloxacin vs placebo[b]	0.44 (0.15 ; 1.25)		
P	0.121		

[a] Allowing for pre-defined ± 6–week window at study visit at 48 weeks

[b] Hazard ratio estimated by adjusting for site, age group and allowing for household clustering

mITT, modified intention-to-treat

Table A5.3. Primary safety analysis[a]

Participants	Levofloxacin	Placebo	Total
All participants receiving ≥ 1 study treatment doses	452	469	921
Grade ≥ 3 adverse events at least possibly associated with study drug			
Number of events	5	8	13
Participants with ≥ 1 event(s)	4 (0.9%)	8 (1.7%)	12
Hazard ratio (95% CI), Levofloxacin vs placebo[b]	0.52 (0.16 ; 1.71), *P* = 0.285		

[a] Analyses based on time to first event.

[b] Hazard ratio estimated adjusting for site, age group and allowing for household clustering.

Table A5.4. All-cause mortality

Number of deaths	Weeks between randomization and death	Age (years)	Cause of death[a]	Attributable to TB[a]	Related to study drug
Levofloxacin					
1	38.9	11 months	Cardiac arrest	Unrelated or unlikely	Unrelated
Placebo					
1	11.3	12 months	Viral pneumonia	Unrelated or unlikely	Unlikely

[a] As adjudicated by the ERC.

Results V-QUIN

Table A5.5. Participant characteristics

Characteristic	Levofloxacin	Placebo	Total
	n (%)	n (%)	n (%)
Total	1023 (100%)	1018 (100%)	2041 (100%)
Age, median age (years, IQR)	41 (28, 52)	39 (28, 53)	40 (28, 52)
< 15	27 (2.6%)	33 (3.2%)	60 (2.9%)
15–29	262 (25.6%)	253 (24.9%)	515 (25.2%)
30–44	290 (28.4%)	324 (31.8%)	614 (30.1%)
45–59	329 (32.2%)	277 (27.2%)	606 (29.7%)
≥ 60	115 (11.2%)	131 (12.9%)	246 (12.1%)
Male gender	374 (36.6%)	361 (35.5%)	735 (36.0%)
Time per day with index case, median h (IQR)	5 (2, 10)	5 (2, 11)	5 (2, 10)
History of TB	56 (5.5%)	50 (4.9%)	106 (5.2%)
Comorbidities			
Diabetes	38 (3.7%)	38 (3.7%)	76 (3.7%)
Chronic kidney disease	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hepatitis B	12 (1.2%)	22 (2.2%)	34 (1.7%)
Hepatitis C	1 (0.1%)	1 (0.1%)	2 (0.1%)
HIV positive	2 (0.2%)	6 (0.6%)	8 (0.4%)
Chronic lung disease	12 (1.2%	8 (0.8%)	20 (1.0%)
TST status			
TST positive	920 (89.9%)	907 (89.1%)	1827 (89.5%)
TST conversion	101 (9.9%)	108 (10.6%)	209 (10.2%)
TST negative and HIV positive	1 (0.1%)	1 (0.1%)	2 (0.1%)
TST negative and body mass index < 16 kg/m^2	1 (0.1%)	2 (0.2%)	3 (0.2%)

IQR, interquartile range; TST, Tuberculin skin test

Table A5.6. Incidence of TB among all participants

Characteristic	Levofloxacin	Levofloxacin-incidence per 100 person-years	Placebo	Placebo incidence per 100 person-years	Incidence rate ratio (95% CI)	*P value*
Intention to treat population	n = 1023		n = 1018			
Completed 30 months follow-up or reached a trial end-point, n (%)	996 (97.4%)	-	999 (98.1%)	-	-	-
Total follow-up, person-years	2586.1	-	2564.6	-	-	-
Bacteriologically confirmed[a], n	6	0.232	11	0.429	0.55 (0.19 ; 1.62)	0.278
Clinically diagnosed only, n	1	0.039	2	0.078	0.49 (0.045 ; 5.46)	0.566
Either bacteriologically confirmed or clinical TB, n (%)	7	0.271	13	0.507	0.54 (0.20 ; 1.46)	0.226

Characteristic	Levofloxacin	Levofloxacin-incidence per 100 person-years	Placebo	Placebo incidence per 100 person-years	Incidence rate ratio (95% CI)	*P value*
Per protocol population	n=700		N=844			
Total follow-up, person-years	1783.7	-	2145.3	-	-	-
Bacteriologically confirmed, n	3	0.168	6	0.280	0.60 (0.15 ; 2.39)	0.474
Clinically diagnosed only, n	0	0.000	1	0.047	Not estimated	-
Bacteriologically confirmed or clinical TB, n	3	0.168	7	0.326	0.52 (0.14 ; 1.99)	0.338

[a] Primary effectiveness outcome

Table A5.7. Adverse events (intention to treat population), per subject

Variable	Levofloxacin (N=1023)	Placebo (N=1018)	Risk difference	*P value*
Participants who took at least one dose of study drug	960 (93.8%)	962 (94.5%)	-0.7 (-3.5, 2.2)	0.65
Participants with one or more adverse events, n (%)				
Total – Any grade 1–4	306 (31.9%)	125 (13.0%)	18.9% (14.2 ; 23.6)	< 0.000
Grade 1 or 2 adverse event	290 (30.2%)	111 (11.5%)	18.7% (14.0 ; 23.3)	< 0.000
Grade 3 or 4 adverse event	29 (3.0%)	19 (2.0%)	1.0% (-0.3 ; 2.4)	0.140
No adverse events	354 (68.1%)	837 (87.0%)	-18.9% (-23.6 ; 14.2)	< 0.000

Secondary safety outcome shown in the shaded row, grade 3–4 adverse events were graded by a blinded expert clinical panel.

Table A5.8. Deaths occurring during and after the treatment period

Variable	Levofloxacin (N=1023)	Placebo (N=1018)	Risk difference (5% CI)	*P value*
Total study population	1023	1018		
Total deaths	4 (0.4%)	3 (0.3%)	0.1 (-0.4 ; 0.6)	0.71
Deaths during treatment period	0 (0%)	0 (0%)		
Deaths occurring after treatment	4 (0.4%)	3 (0.3%)	0.1 (-0.4 ; 0.6)	0.71
Cause of death: TB related	0 (0%)	0 (0%)	Not estimated	Not estimated
Cause of death: Cancer	2 (0.2%)	0 (0%)	Not estimated	Not estimated
Cause of death: Stroke	0 (0%)	2 (0.2%)	Not estimated	Not estimated
Cause of death: Uncertain	2 (0.2%)	1 (0.1%)	Not estimated	Not estimated

Cause of death assigned at verbal autopsy conducted at completion of the study follow-up period

Table A5.9. TPT completion

Variable	Levofloxacin n (%)	Placebo n (%)	Risk difference (%) (Levofloxacin vs placebo)	*P value*
Total	N = 1023	N = 1018		
Treatment completed	700 (68.4%)	844 (82.9%)	-14.5% (-19.4 ; -9.6)	< 0.001
Treatment not completed for any reason	323 (31.6%)	174 (17.1 %)		
Death during treatment, not related to therapy	0 (0%)	0 (0%)	0 (0)	Not applicable
Diagnosis of active TB during treatment	0 (0%)	4 (0.4%)	-0.4%	Not applicable
Never started therapy, participant's decision	63 (6.2%)	56 (5.5%)	0.7% (-2.2 ; 3.5)	0.65
Took at least 80% of treatment (144 doses) in > 270 days	16 (1.6%)	17 (1.7%)	-0.1% (-1.3 ; 1.1)	0.858
Stopped due to participant's decision, but not a medical decision	237 (23.2%)	93 (9.1%)	14.0% (10.1 ; 17.9)	< 0.0001
Stopped due to a medical decision	7 (0.7%)	4 (0.4%)	0.3 (-0.3 ; 0.9)	0.365
Therapy stopped permanently due to adverse events[a]				
Any adverse event	71 (6.9%)	11 (1.1%)	6.0% (4.0 ; 7.7)	< 0.0001
Grade 1 or 2 adverse event	61 (6.0%)	7 (0.7%)	5.3 % (3.5 ; 7.0)	< 0.0001
Grade 3 or 4 adverse event	12 (1.2%)	4 (0.4%)	0.8% (-0.2 ; 1.5)	0.043
Death	0 (0%)	0 (0%)	0 (0%)	-

[a] One participant stopped due to both a grade 3–4 and grade 1–2 adverse events.

Overall trial conclusions

TB CHAMP

- Evidence of Lfx efficacy with substantial effect size: 1.1% in Lfx arm vs 2.6% in placebo arm (HR, 0.44 [95% CI 0.15 ; 1.25])
- Stronger evidence of treatment effect in site-assessed end-points and Bayesian analysis
- Lfx extremely safe in children: only 6 children in Lfx arm discontinued treatment early due to AEs compared, with 1 in the placebo arm
- Rate TB end-points lower than expected
- A high proportion of children were screened out with presumptive TB
- Lower IGRA positivity than expected. Power calculation assumed 40%+ vs 20%.

V-QUIN

- Lfx associated with a 45% reduction in microbiologically confirmed incident TB at 30 months.
- Few event resulted in broad confidence limits in the primary analysis, which spanned the null (not statistically significant)
- The incidence of grade 3–4 AEs was low, and no difference was seen between groups
- No acquired drug resistance to Lfx was observed
- About three times as many co-prevalent as incident TB cases
- In a sub-study, microbiome diversity was persistently reduced 6 months after therapy, with an increase in nasal carriage of FQ-resistant *Staphylococcus aureus*, a type associated with greater virulence

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

Harsimren Sidhu, Siobhan Carroll, Dick Menzies[9]

Introduction

Two randomized trials (V-QUIN and TB CHAMP) investigating safety, efficacy and tolerability of 6-month daily Lfx (6Lfx) treatment as TPT for individuals exposed to multidrug-/rifampicin-resistant tuberculosis (MDR/RR-TB) were completed in 2023. The aim of this review was to systematically review other published data from trials or observational studies on the efficacy, safety and tolerability, completion, acceptability, resource requirement, feasibility of implementation, cost-effectiveness and impact on equity of FQ regimens for TPT among all MDR/RR-TB contacts, to inform the Guideline Development Group tasked to revise the WHO TPT guidelines in December 2023. This review updated one conducted in 2016 to inform the 2018 WHO TPT guideline. The scope included studies of the efficacy and safety of other TPT regimens for MDR/RR-TB.

Methods

Research questions

1. What are the efficacy, safety, tolerability, acceptability, resource requirement, feasibility, cost-effectiveness and impact on equity of Lfx (or moxifloxacin (MFX) given as TPT in people of all ages and settings exposed to MDR/RR-TB?
2. What are the safety and efficacy of all other TPT drug regimens for individuals in contact with MDR/RR-TB patients?

For both objectives, searches were performed in PubMed, Embase, Turning Research Into Practice (TRIP) and the Global Health Library. For randomized trials, the Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. No language restriction was set for any of the searches. Relevant studies were also identified in the reference lists of relevant studies.

Inclusion criteria

Objective 1:

- Use of FQ (Lfx/MFX) TPT for contacts of MDR/RR-TB index patients.
- At least one of the following outcomes reported: TB disease incidence, change in TB-related and all-cause mortality, adverse events, treatment completion rate, emergence of additional FQ resistance in TB strains or in the microbiome other than TB strains, resources required for implementation, impact on equity, patient and health-care worker values and acceptability of FQ-based TPT, cost-effectiveness and feasibility.
- Study designs: any longitudinal design (cohorts, case–control studies, case series, population-based observational studies), cost-effectiveness modelling and RCTs.

Objective 2:

- Must include one of the following TPT regimens: 6 or 9H, 12H, 18–36H, 3 or 4HR, 1HP, 3HP, 4R, bedaquiline, delamanid, ethambutol (EMB), ethionamide/ protionamide (ETH/PTH) or other recommended TPT regimens (not Lfx or MFX).

[9] McGill International TB Centre & WHO Collaborating Centre in TB Research, Montreal Chest Institute, and Research Institute of the McGill University Health Centre

- Must include one of the following outcomes: TB disease incidence, prevention of disease, estimated TB-related and all-cause mortality and risk of adverse events.
- Study design: randomized control or observational studies.

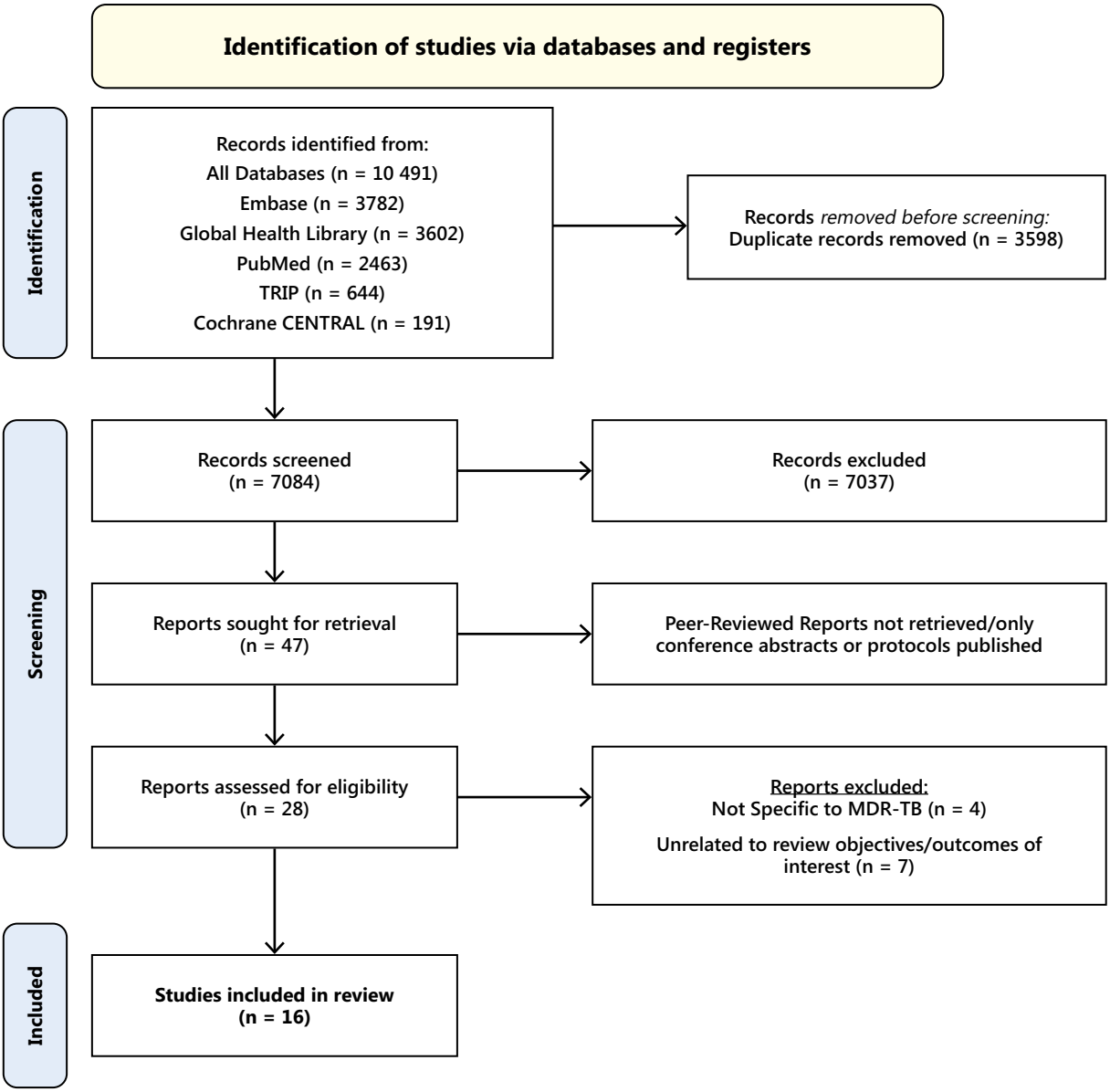
Exclusion criteria

Literature reviews, abstracts, case reports, opinion articles, grey literature. For objective 2 specifically, studies that did not provide denominators to allow estimates of TB disease incidence or incidence (risk) of adverse events or had fewer than 20 participants.

Quality assessment of included studies

Two reviewers independently evaluated the design and the quality of the evidence in the included articles. Differences were resolved through discussion until a consensus was reached. For observational studies, a quality assessment questionnaire was developed to evaluate bias with items from the Newcastle–Ottawa Scale *(1)*. The cross-sectional studies (with acceptability as the outcome) were evaluated using the AXIS tool and the one cost-effectiveness study included was evaluated using the Joanna-Briggs Institute critical appraisal tool for economic evaluations *(2,3)*. All studies were categorized into either "high", "medium", or "low" risk of bias for all items on the quality assessment forms. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework was used to evaluate the quality of study evidence.

Fig. A5.3. PRISMA flow diagram of screening



No RCTs were found. All the studies included were observational, and no studies of resource requirements, feasibility or impact on equity were found. Four of the 16 studies included efficacy: one with MFX or ofloxacin (OFX) monotherapy, two with Lfx or MFX with a companion drug (ETH, EMB or PZA and one with standard INH therapy. Five studies reported on safety outcomes, four of which were of children and adolescents and one of adult contacts. Six studies reported the acceptability of FQ-based TPT; five reported quantitative measures and one the qualitative acceptability of a novel paediatric Lfx formulation to caregivers and child contacts. One study evaluated the global cost-effectiveness of providing Lfx to HHCs < 15 years. The studies included were too disparate to allow any pooling of results or meta-analyses. Therefore, the results below reflect non-pooled findings. The protocol of this systematic review was registered on Prospero on 23 September 2023 (ID: CRD42023462793).

Results and quality of evidence

Efficacy of TPT regimens for contacts exposed to MDR-TB

Table A5.10. Observational studies evaluating the efficacy of FQ-based TPT regimens to prevent TB among HHCs of MDR-TB patients

Reference	Setting	Population	Intervention(s)	Control(s)	Outcome definition	Proportion of participants who developed TB disease
Studies of TPT including child and adolescent HHCs of patients with MDR-TB						
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Household contacts aged < 18 years (n=72)	9MFX (n=55)[a]	Child contacts with caregivers who refused TPT (n=14)	People with culture-confirmed TB within 2 years of follow-up	MFX: 0/55 Refused TPT: 1/14
Malik et al. (2021) *(5)*	Karachi, Pakistan	Household contacts of all ages (n=799)	6-month FQ (Lfx/MFX) + ETH/EMB (n=172)	Refused TPT (n=43) Considered ineligible for TPT (n=574)	People with culture-confirmed TB within 2 years of follow-up	Any TPT: 2/172 Refused TPT: 0/43 Ineligible: 0/574
Studies of TPT among close adult contacts of MDR-TB						
Bedini et al. (2016) *(6)*	Penitentiary in Modena, northern Italy	Incarcerated adults in close contact with MDR-TB (n=17)	6-month Lfx + PZA (n=12)	Refused TPT (n=5)	People with incident TB disease during 24 months of follow-up	Lfx + PZA: 0/12 Refused TPT: 0/5

9MFX, 9 months of moxifloxacin; FQ, fluoroquinolone; Lfx; levofloxacin; MDR-TB, multidrug-resistant TB; ETH, ethionamide; EMB, ethambutol; PZA, pyrazinamide.

[a] Three participants were treated for 9 months with ofloxacin but are not cited here due to stronger evidence from other studies with different estimates of efficacy.

Overall, the studies show that FQ-based TPT is not associated with a significant reduction of TB disease. Quality assessment suggests considerable risk of selection bias and small sample sizes, making estimates of efficacy imprecise. Gureva et al. *(4)* used a very small comparator group and was biased, as refusal was likely to be associated with other factors that affect health outcomes. INH was found to be effective for MDR-TB contacts in the study by Huang et al. *(7)* (incident TB aHR 0.19) conducted among children and adolescents < 19 years in Lima, Peru (see Table A5.11); however, potential selection bias in this study was high. The reason why the comparator group was untreated with INH is unclear but was presumably due to refusal. The mean duration of INH treatment was 115 days due to cessation TPT when multidrug resistance was confirmed, which is significantly shorter than the usual 180 days.

Table A5.11. Summary of a prospective cohort study evaluating of the efficacy of INH TPT for HHCs of MDR-TB index patients *(7)*

Reference	Setting	Population	Intervention	Control	Type of outcome	People who developed TB disease / person-years of follow-up
Huang et al. (2020) *(7)*	Lima, Peru	Children/ adolescents aged ≤ 19 who were HHCs of MDR-TB index patients (n=666)	INH[a] (n=265)	No INH (n=401)	Culture-confirmed TB disease per person-year (≥ 1 year of follow-up)	**Overall** INH: 3/320 No INH: 23/474 aHR[b], 0.19 [95% CI, 0.05 ; 0.66] Child contacts (< 5 years) INH: 2/144 No INH: 10/145 HR, 0.19 [95% CI, 0.04 ; 0.98]

HHCs, household contacts; aHR, adjusted hazard ratio; INH, isoniazid

[a] Duration of treatment varied among participants, as some were told by their physicians to stop treatment after MDR-TB confirmation.

[b] Hazard ratio adjusted for index case age, recreational drug use, HHC, age, sex, bacillus Calmette-Guérin vaccination scar, nutritional status, being a student, TB history, household socioeconomic status and household residential district.

Safety of TPT regimens used among MDR-TB contacts

Table A5.12. Summary of studies evaluating the safety of FQ-based TPT regimens for children and adolescent (< 18)

Reference	Setting	Population	Intervention(s) or exposure(s)	Outcome(s) reported	Outcome estimate
Apolisi et al. (2023) *(8)*	Khayelitsha, Cape Town, South Africa	Children and adolescents aged 0–18 years who were s HHC of an MDR-TB index case (n=95)	6Lfx (n=79) or 6INH (n=9)	Mild or moderate AE reported during TPT Serious AE Treatment discontinuation due to drug-related AE	6Lfx: 8/79 6INH: 0/9 None 6Lfx: 3/79 6INH: 0/9
Garcia-Prats et al. (2019) *(9)*	Cape Town, South Africa	Children < 5 years who were HHC of an MDR-TB index case (n=27)	Short-term pharmacokinetics provision of novel 100 mg paediatric Lfx dispersible tablets	Grade 1 or 2 AE at least possibly related to Lfx Grade 3 or 4 AE at least possibly related to Lfx Lfx discontinuation due to drug-related AE	2/27 0/27 0/27
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Children aged < 18 years who were HHC of an MDR-TB index case (n=72)	9MFX (n=55) or 9OFX (n=3)	Grade 1 or 2 drug-related AE Treatment discontinuation due to drug-related AE Proportion completing TPT	6/58 1/58 52/58 (90%)
Malik et al. (2020;2021) *(10,11)*	Karachi, Pakistan	HHC of all ages exposed to MDR-TB index case (n=172)	6-month ETH + FQ (Lfx or MFX) (n=59) 6-month EMB + FQ (Lfx or MFX) (n=113)	Grade 1 or 2 drug-related AE Children < 5 years who reported AE Treatment discontinuation due to drug-related AE Proportion completing TPT	ETH + FQ: 20/59 EMB + FQ: 16/113 6/61 11/172 (6%) 121/172 (70%)

6Lfx, 6-months of levofloxacin; 6INH, 6 months of isoniazid; 9MFX, 9 months of moxifloxacin; 9OFX, 9 months of ofloxacin; HHC, household contacts

Of the five studies evaluating the safety of FQ-based TPT among exposed MDR-TB contacts, three reported AE and treatment discontinuation after FQ monotherapy with either Lfx, OFX or MFX alone (Table A5.12). No serious or grade 3/4 AE were reported in these studies and very low discontinuation of FQ treatment. The AE rates were higher in the study of Malik et al. *(10)*, in which Lfx/MFX was given with ETH or EMB, and in the study by Bedini et al. *(6)* in which contacts received Lfx and PZA (Table A5.13). Malik et al. found a higher proportion of grade 1 or 2 AE with ETH than with EMB, and 11 of the 36 contacts discontinued TPT. Similarly, in the study by Bedini et al. *(6)*, the combination of Lfx and pyrazinamide was poorly tolerated.

Table A5.13. Summary of study evaluating the safety of FQ-based TPT regimens among adult HHCs of MDR-TB index patients

Reference	Setting	Population	Intervention/ exposure	Outcomes reported	Outcome estimates
Bedini et al. (2016) *(6)*	Penitentiary in Modena, northern Italy	Incarcerated adults in close contact with MDR-TB case (n=17)	6-month Lfx + PZA (n=12)	Any AE Treatment discontinuation due to drug-related AE Completed 6-month TPT regimen	9/12 7/12 (58%) 5/12 (42%)

AE, adverse events; Lfx, Levofloxacin; MDR-TB, multidrug-resistant TB; PZA, Pyrazinamide; TPT, TB preventive treatment

The objective of the review was to determine the safety of FQ in MDR prevention or treatment. Data from three studies that reported AEs attributable to Lfx or MFX were retrieved. A study by Ali et al. *(12)* addressed acute Fridericia-corrected QT interval (QTcF) responses to experimentally administered TB drugs, including Lfx and MFX, either alone or in combination with another drug. MFX given alone resulted in only one mild (grade 1) QTcF prolongation in 32 patients, and Lfx alone resulted in QTcF prolongation in 19 patients. A pharmacokinetics study by Jin et al. *(13)* reported a significant association between higher Lfx concentration and increased QTc intervals; however, the QTc intervals decreased over time, and there was no significant difference from pre-treatment intervals by the end of 12 months. Treatment was not discontinued in any patient, and no patients experienced cardiac adverse events. A study conducted by Garcia-Prats et al. *(14)* among 70 children aged < 15 years treated for MDR-TB disease found a significant number of grade 1 AE (59/70) and grade 2 AE (11/70) that were related to Lfx. Only one child experienced a grade 3 AE, and no children experienced grade 4 AE. Treatment was not discontinued.

Acceptance, willingness and acceptability of FQ-based TPT regimens

For this review, two quantitative and one qualitative outcome were considered for acceptance (actually starting), stated willingness to start (theoretical) and acceptability according to on qualitative methods. Acceptance was defined as the proportion of eligible contacts who accepted and started TPT when offered.

Table A5.14. Summary of studies of acceptance to start FQ-based TPT among caregivers and MDR-TB HHCs

Reference	Setting	Population	Intervention	Outcome definition	Acceptability: agreed to start
Gureva et al. (2022) *(4)*	Arkhangelsk Region, Russian Federation	Children < 18 years who were HHCs of an MDR-TB index case (n=72)	9-month FQ (MFX or OFX)	Proportion of caregivers who agreed for a child to start TPT with OFX/MFX	58/72 (81%)
Malik et al. (2021) *(5)*	Karachi, Pakistan	Household contacts of all ages exposed to an MDR-TB index case (n=215)	6-month FQ (Lfx or MFX) + ETH or EMB	TPT-eligible participants who accepted to start treatment	172/215 (80%)

ETH, ethionamide; EMB, ethambutol; FQ, fluoroquinolone; HHC, household contacts; Lfx, levofloxacin; MFX, moxifloxacin; OFX, ofloxacin; TPT, TB preventive treatment

The reported degree of acceptance in these two studies was relatively high (Table A5.14). Gureva et al. *(4)* reported acceptance of 81% with MFX or OFX and Malik et al. found 80% acceptance of Lfx or MFX and a companion drug (ETH or EMB). Strong willingness was noted among adult and adolescents (Table A5.15), which, however, dropped for TPT that had potential side-effects.

Table A5.15. Studies of willingness to start hypothetical fluoroquinolone-based TPT among caregivers and MDR-TB HHCs

Reference	Setting	Population	Outcome definition	Acceptability: willingness to start
Rouzier et al. (2022) *(15)*	Botswana (1 site), Brazil (1), Haiti (1), India (2), Kenya (1), Peru (2), South Africa (7), Thailand (1)	Adult and adolescent HHC who reported caring for children < 13 years of age (n=299)	Proportion of caregivers willing to administer daily TPT pill to their children have their children complete prerequisite steps to determine MDR TPT eligibility	278/299 (93%) 283/299 (95%)
Suryavanshi et al. (2019) *(16)*	Same as above	Adolescent and adult HHC of MDR-TB index cases (n=743)	Percentage of HHC willing to take a hypothetical, newly developed TPT take TPT with potential mild, temporary side-effects	79% 70%

HHC, household contacts; MDR-TB, multidrug-resistant TB; TPT, TB preventive treatment

The acceptability of Lfx, i.e. willingness and ability to adhere to a TPT regimen, was addressed in two studies of a novel child-friendly Lfx formulation. Purchase et al. *(17)* found high acceptability among children and their caregivers; for example, 81% of caregivers found the formulation easier to prepare than the adult formulation, and 82% found the size of the tablet to be acceptable. Wademen et al. *(18)* also found high acceptability, although caregivers expressed concern about the financial and care burden, especially when they themselves were on treatment for MDR-TB disease.

Cost-effectiveness of TPT among children exposed to MDR-TB

The cost-effectiveness of several contact management strategies was examined by modelling in a study by Dodd et al. *(19)* (Table A5.16). The authors reported that provision of TPT with screening and treatment of co-prevalent TB disease was more cost-effective than detection and treatment of disease among HHCs of MDR-TB patients alone. TPT for groups at highest risk was the most cost-effective strategy, and providing TPT to all children under 15 averted most deaths and the greatest reduction in life-years lost. When the analysis was updated with efficacy estimates from the TB CHAMP and V-QUIN trials, the results were similar (unpublished data provided by J. Seddon).

Table A5.16. Summary of Dodd et al. *(19)* global modelling study on the cost-effectiveness of several MDR-TB HHC management scenarios for children < 15 years

Household contact management scenario	Life-years lost, 3% discounted (thousands)	Total deaths averted	Deaths averted with TPT provision	ICER (US$ per DALY)
No detection or treatment of co-prevalent TB disease; no TPT (baseline scenario)	171	–	–	–
Detection and treatment of co-prevalent TB disease for HHCs aged < 15; no TPT	105	2350	–	960
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 5 and children < 15 with HIV	80.6	3220	870	738
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 5 years and children < 15 with HIV or TST-positive	72.6	3510	1160	773
Detection and treatment of co-prevalent TB disease; TPT (6Lfx/6MFX) for all children < 15	70.3	3590	1240	838

6Lfx, 6 months of levofloxacin; 6MFX, 6 months of moxifloxacin; HHC, household contacts; ICER, incremental cost-effectiveness ratio; DALY, disability-adjusted life year; TPT, TB preventive treatment; TST, tuberculin skin test

Conclusion

No randomized controlled trials that addressed the objectives of this systematic review were identified. Hence, no high-quality evidence on the efficacy of FQ-based TPT for MDR-TB contacts was found. All the observational studies identified had problems of selection bias and small samples; none suggested any significant benefit of use of FQ-based TPT to prevent development of MDR-TB disease. Although the quality of evidence was low, the results from larger observational studies suggest that FQ-based TPT is safe for use among MDR-TB contacts. No grade 3, 4 or serious adverse events related to Lfx or MFX were reported, and FQ monotherapy had high completion rates and acceptability. Mild or moderate adverse events were observed in children and adolescents. A high-quality modelling study evaluating cost-effectiveness found that targeting the highest risk groups – children < 5 or < 15 years with HIV – was the most cost-effective, but provision of FQ TPT to all contacts < 15 years would have greater impact and still be more cost-effective than detection of prevalent TB disease alone. Higher quality evidence is necessary on the efficacy of FQ-based TPT for prevention of MDR-TB disease among contacts.

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A5.3 Assessing fluoroquinolone (levofloxacin) acceptability among contacts of MDR-TB patients: a qualitative study[10]

Objective: to assess the values, preferences, acceptability and feasibility of Lfx as TPT for adult HHCs of patients diagnosed with MDR-TB in five low- and middle-income countries: Georgia, India, Indonesia, South Africa and Viet Nam.

Sampling and recruitment strategy: Eligible participants who were contacts of newly diagnosed MDR-TB patients were identified in the five countries. In South Africa and Viet Nam , collaborators also recruited participants who were part of the V-QUIN and TB CHAMP trials, including participants who did and did not complete the study treatment due to adverse events. Collaborators at each site explained the project briefly to potential participants. Interviews were conducted in the presence of a skilled interpreter where required. Informed consent, written or verbal, was obtained before the interview.

Eligibility criteria

Inclusion:

- household contact of a person diagnosed with MDR-TB.
- eligible for TPT according to WHO guidelines *(1)*.

Exclusion:

- < 18 years
- unable to provide informed consent
- unable to be interviewed in Cantonese, English, French, Mandarin or Punjabi or interpreter not available.

Methods

A trained qualitative researcher conducted one-on-one interviews with a semi-structured interview guide with the participants over telephone or online. Trained interpreters, hired by the interviewers, were present when required. The interviews lasted 30–60 min. The interviewer asked participants about their attitude, values and perspectives towards use of FQs as TPT and sought to understand the risk–benefit considerations underlying their decisions. Participants were informed of the estimates of effectiveness and side-effects from the preliminary results of the randomized trial study populations in Viet Nam (adults) and South Africa (children). They were also informed about the risks of MDR-TB disease, and the difference from TB infection, and risks and burden of MDR-TB treatment, including treatment duration, adverse events and treatment outcomes. This allowed participants to make an informed decision on whether they preferred TPT to an increased risk of developing MDR-TB disease. Interviewers at each site recorded demographic and clinical information, including age, sex, level of education, comorbidities and TB history on a patient enrolment form. Data were analysed with an inductive approach. Thematic analysis was used to identify and highlight recurring themes.

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Table A5.17. Study participants (n=36)

Characteristic	n	% or range
Country		
Georgia	7	19
India	10	28
Indonesia	5	14
South Africa	9	25
Viet Nam	5	14
Female	19	53
Median age (years)	41	21–67
Employed	22	61
Chronic condition[a]	11	31
Offered TPT[b]	9	25
Accepted	6	17

[a] Diabetes, cardiovascular disease, chronic gastritis, joint pain/arthritis, HIV

[b] 2/2 were offered and accepted TPT for DS-TB, 4/7 were offered and accepted TPT for MDR-TB (6-month Lfx).

Results

A total of 36 participants were interviewed (Table A5.17).

Acceptability of TPT for MDR-TB involved a decision on whether:

- TPT held value for them ("values");
- TPT effectiveness, requirements and safety met their subjective thresholds ("preferences"); and
- they anticipated being able to complete the treatment successfully ("feasibility").

The participants' values were influenced by their sociocultural and economic contexts, as well personal and community experiences with MDR-TB. The values aligned with higher TPT acceptability included:

- belief in the importance of disease prevention, such as vaccination;
- general trust in medicines and doctors, "The doctor knows best, so whatever they give, I have to take." (India, 45-year-old woman);
- fear of MDR-TB disease, its treatment and contagiousness, "I would feel so bad if I got MDR-TB, it will be very painful….TPT is a good thing because I have younger grandkids and we don't know when they will catch it." (South Africa, 50-year-old woman).
- A participant's values could override the perceived benefits and harms of TPT. For instance, a few participants who did not value disease prevention would refuse MDR TPT, regardless of its potential effectiveness, low requirements and safety, unless it was mandatory.

Among participants who found value in TPT, acceptance depended on their subjective thresholds for treatment effectiveness, dosage and schedule and adverse drug reactions. For instance, participants would tolerate mild-to-moderate side-effects and long treatment duration, if they had a minimum level of efficacy (such as reducing the risk of disease by 50%), but not if TPT efficacy was below that threshold. Given an acceptable level of efficacy, most participants prioritized safety over treatment duration; treatment schedule was considered the least important. The final consideration of acceptability was perceived feasibility. Participants who valued TPT reflected on demands on their lives due to TPT. They considered the following as potential barriers: out-of-pocket expenses (e.g. transport); disruption due to clinical follow-up, time commitment and requirement for child-care arrangements; lack of social and financial support; and insufficient treatment counselling and education.

Overall, MDR TPT was acceptable and held a high social value among participants in the five settings. The most acceptable regimen would have high effectiveness in preventing MDR-TB, mild toxicity, little interference with daily activities, low pill-burden, minimal and convenient clinical follow-ups, and low cost to the participants.

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A5.4 A survey to explore the programmatic feasibility of levofloxacin (Lfx) TPT for MDR-TB contacts[11]

Introduction

The survey assessed the feasibility of programmatic use of Lfx for TPT among contacts of MDR-TB patients in the eventuality of a WHO recommendation for its programmatic use. The objective was to collect perspectives from national TB programmes (NTPs), explore current practices for MDR TPT, its programmatic feasibility, affordability, impact on equity, acceptability to patients and health-care workers and to inform the discussion of WHO Guideline group at its meeting on 4–6 December 2023.

Methods

Sampling and recruitment strategy: Purposive sampling of NTP managers in 30 countries listed by the WHO as having the highest burden of MDR-TB who were contacted from publicly listed e-mail addresses. 18 programme managers responded within the expected timeline, comprising three in the WHO African Region, two in the South-East Asia Region, seven in the European Region, one in the Eastern Mediterranean Region, and five in the Western Pacific Region. The perspectives of NTP managers were collected on a self-administered, short-answer survey questionnaire sent by e-mail.

Results

Current practice in use of MDR TPT among contacts of DR/MDR-TB patients: Seven (39%) of 18 NTP managers reported use of 6Lfx for MDR-TB contacts, although in two countries use was limited due to high background resistance to FQs. One respondent each reported use of 9-month Lfx as a part of a two-drug regimen with either ethionamide or prothionamide as a companion drug, high-dose INH and either 6-month standard dose INH or 3 months of once-weekly INH and rifapentine. Three (17%) did not specify the TPT regimen being used. Eight (44%) respondents reported no use of TPT for contacts of DR/MDR-TB patients.

Affordability: Respondents were informed about the estimated cost of providing 6Lfx at the Global Drug Facility price per treatment course (approximately US$ 18.50, as compared with 6H at US$ 3.50 and 9H at US$ 5.25). Most respondents considered 6Lfx to be affordable. Nine (50%) stated that it would be affordable for all ages, three (17%) that it would be affordable only for HHCs < 15 years and one (6%) only for HHCs < 5 years. Three (17%) respondents stated that 6Lfx would not be affordable and two (11%) that it would depend on the availability of donor funding.

Programmatic feasibility (additional resources required, distribution, training, timeline): Nine (50%) of the 18 respondents suggested that the cost and the availability of additional resources would not be barriers to implementation, while seven (39%) considered that additional funding would be necessary for expansion of drug-susceptibility testing, contact screening, monitoring and follow-up for individuals started on TPT. Five (28%) respondents noted that implementation of 6Lfx TPT would divert resources from other services and called for proactive planning. All the managers stated that logistics management for Lfx would be sustainable. Nine (50%) managers stated that no training or < 12 h of additional training would be required for health-care workers, and four (22%) respondents said that > 12 h of training would be necessary.

With regards to the timeline for nationwide scaling up of 6Lfx TPT, nine (50%) respondents estimated that it would take <3 years and one (6%) stated >3 years. The others either did not provide information or were unsure. Acceptability to health-care workers was generally anticipated to be high, five (28%) respondents expected health-care workers to remain neutral, some expressed concern about fear

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of Lfx resistance by health-care workers and that TPT uptake remains low among contacts of drug-susceptible TB patients. Acceptability among recipients was also anticipated to be relatively high given the severity of MDR-TB disease, stigmatization and resulting socioeconomic challenges. Other challenges may include lack of community awareness, long duration of TPT and potential side-effects.

Equity considerations: NTP managers expected equity to be increased due to prevention of MDR-TB disease, although six (33%) respondents expressed concern about access in remote locations, and two mentioned a risk of drug shortages if computation of requirements is based on notification data. Eleven (61%) respondents also raised concern about increased out-of-pocket spending for contacts, and two (11%) mentioned that health insurance does not cover TB treatment.

Implementation decisions: Seven respondents reported current use of 6Lfx, and eight expressed willingness to implement it immediately or after a few years provided WHO made a strong recommendation. Only two (11%) respondents stated that they would not implement 6Lfx despite a strong recommendation. In the case of a conditional WHO recommendation, seven (39%) respondents stated that programmatic implementation was less likely, while some mentioned slow or staggered implementation or faster introduction in some regions than in others.

Conclusion

Most national programme managers were willing to use 6Lfx for MDR-TB contacts after a strong WHO recommendation. 6Lfx is anticipated to be generally affordable and feasible, would increase equity and would be acceptable to both health-care workers and contacts. Specific concerns of national programme managers were constraints in funding, human and other resources, fear of increased Lfx resistance and increased out-of-pocket spending, which would reduce equity. Although not all countries responded, those that did can be considered reasonably representative. As this was a short cross-sectional, self-administered survey, broader programmatic perspectives of NTP managers about the affordability or feasibility of obtaining additional resources could not be evaluated.

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