WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection

Web Annex B. GRADE profiles

Third edition

WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, third edition. Web Annex B. GRADE profiles

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Contents

Abbreviations and acronyms

AlereLAM	**Alere Determine™ TB LAM Ag**
CI	confidence interval
CRS	composite reference standard
CSF	cerebrospinal fluid
FIND	Foundation for Innovative New Diagnostics
FL-LPA	first-line line probe assay
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
LAM	lipoarabinomannan
LAMP	loop-mediated isothermal amplification
LF-LAM	lateral flow urine lipoarabinomannan assay
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MRS	microbiological reference standard
NGS	next-generation sequencing
QUADAS	quality assessment of diagnostic accuracy studies
SL-LPA	second-line line probe assay
SLID	second-line injectable drug
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

2.1 Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles: Xpert MTB/RIF and Xpert Ultra

Table 1.: Xpert MTB/RIF compared to smear microscopy in adults with signs and symptoms of pulmonary tuberculosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Xpert MTB/RIF	smear microscopy	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5 [1,2,3,4,5]	randomised trials	not serious [a]	not serious [b]	not serious	serious [c]	none	248/5265 (4.7%)	292/5144 (5.7%)	**RR 0.88** (0.73 to 1.05)	**7 fewer per 1,000** (from 15 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cure												
2 [3,6,7]	randomised trials	not serious	not serious	not serious [d]	not serious	none	1786/2500 (71.4%)	1443/2080 (69.4%)	**OR 1.09** (1.02 to 1.16)	**18 more per 1,000** (from 4 more to 31 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Pre-treatment loss to follow up												
3 [3,4,5]	randomised trials	not serious	serious [3,4,5,e]	not serious	not serious	none	81/642 (12.6%)	95/523 (18.2%)	**RR 0.59** (0.42 to 0.84)	**74 fewer per 1,000** (from 105 fewer to 29 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Time to diagnosis												
2 [2,5]	randomised trials	not serious [a]	not serious	not serious [f]	not serious [g]	none	956 participants	968 participants	**HR 1.05** (0.93 to 1.19) [Time to diagnosis]	**5 more per 1,000** (from 7 fewer to 18 more)	⨁⨁⨁⨁ HIGH	CRITICAL
							-	10.0%		**5 more per 1,000** (from 7 fewer to 18 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Xpert MTB/RIF	smear microscopy	Relative (95% CI)	Absolute (95% CI)		
Time to treatment												
4 [2,3,4,5]	randomised trials	not serious [a]	not serious	not serious [f]	serious [h]	none	4055 participants	4153 participants	**HR 1.00** (0.75 to 1.32) [Time to treatment]	**0 fewer per 1,000** (from 24 fewer to 30 more)	⨁⨁⨁◯ MODERATE	CRITICAL
							-	10.0%		**0 fewer per 1,000** (from 24 fewer to 30 more)		
Mortality in HIV-positive participants												
2	randomised trials	not serious	not serious	not serious	serious [i]	none	66/1211 (5.5%)	75/1055 (7.1%)	**RR 0.76** (0.59 to 1.00)	**17 fewer per 1,000** (from 29 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
New outcome												
									not estimable		-	

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

Explanations

a. For all randomized trials, blinding of physicians to what test was done was impossible since knowing which test was done is part of the intervention itself. For example, the Xpert test has higher sensitivity than smear microscopy (and also produces RIF resistance results) and physicians must be allowed to take this into account when deciding about patient management. While outcomes between patients may therefore be different due to lack of blinding this was not judged to be a source of bias but rather the mechanism through which the intervention had an effect. Outcome measurement could theoretically have been influenced by the lack of blinding but this was deemed unlikely to cause bias of important magnitude. Overall, the lack of blinding was therefore judged not to put studies at increased risk of bias.Type a message

b. No evidence of inconsistency, four studies in the direction of showing benefit.

c. The 95% CI is wide likely suggesting imprecision. We caution about interpreting non-significance as no effect when the CI likely includes an effect that may be clinically important. We downgraded one level for Imprecision.

d. Cure is the outcome of interest for patient important outcome. Studies have reported treatment success which includes those cured and those completing treatment without evidence for treatment failure . However, we did not downgrade for indirectness

e. Variability in time for assessment of pre-treatment loss to follow up; Churchyard 2015 assessed within 28 days after enrolment, Cox 2014 assessed by three months after enrolment and Theron 2014 assessed by the end of the study (six months)

f. The results are from trials that directly compared the populations, interventions and outcomes of interest. We did not downgrade for imprecision

g. The results suggest that Xpert did not improve time to diagnosis compared to smear microscopy but the direction of effect is towards benefit. We did not downgrade for imprecision because the 95% CI is narrow.

h. The results suggest that Xpert did not improve the time to treatment comapred to smear microscopy. The 95% CI is wide likely suggesting imprecision

i. Similarly, the 95% CI is wide likely suggesting imprecision. We caution about interpreting non-significance as no effect when the CI likely includes an effect that may be clinically important. We downgraded one level for Imprecision.

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Table 2: Should Xpert MTB/RIF be used to diagnose pulmonary TB in adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.85 (95% CI: 0.82 to 0.88)
Specificity	0.98 (95% CI: 0.97 to 0.98)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary TB)	70 studies 10.409 patients	cross-sectional (cohort type accuracy study)	not serious [1]	not serious [a]	not serious [b]	not serious [c]	none	21 (21 to 22)	85 (82 to 88)	255 (246 to 264)	⨁⨁⨁⨁ HIGH
False negatives (patients incorrectly classified as not having pulmonary TB)								4 (3 to 4)	15 (12 to 18)	45 (36 to 54)	
True negatives (patients without pulmonary TB)	70 studies 26.828 patients	cross-sectional (cohort type accuracy study)	not serious [1]	not serious [a]	not serious	not serious	none	956 (946 to 956)	882 (873 to 882)	686 (679 to 686)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary TB)								19 (19 to 29)	18 (18 to 27)	14 (14 to 21)	

Explanations

a. The median tuberculosis prevalence in the studies was 27%.

b. For individual studies, sensitivity estimates ranged from 43% to 100%. We thought that differences in enrolment criteria (different populations targeted), disease severity, and setting could in part explain heterogeneity. We did not downgrade for inconsistency.

c. There were a large number of studies and participants in this analysis. The 95% CrI around true positives and false negatives would probably not lead to different decisions depending on which credible limits are assumed. We did not downgrade for imprecision.

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Table 3: Should Xpert Ultra be used to diagnose pulmonary tuberculosis in adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.90 (95% CI: 0.84 to 0.94)
Specificity	0.96 (95% CI: 0.93 to 0.97)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	6 studies 960 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	22 (21 to 23)	90 (84 to 94)	269 (253 to 281)	⨁⨁⨁⨁ HIGH
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								3 (2 to 4)	10 (6 to 16)	31 (19 to 47)	
True negatives (patients without pulmonary tuberculosis)	6 studies 1694 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	932 (902 to 951)	860 (833 to 878)	669 (648 to 683)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary tuberculosis)								43 (24 to 73)	40 (22 to 67)	31 (17 to 52)	

Explanations

a. We considered 4/6 studies, accounting for 82.2% of the participants in this analysis, to be applicable to the review question. In Chakravorty 2017, 63% of participants had pulmonary TB; however this study accounted for only 10.4% of the total participants in this analysis. In Opota 2019, information about clinical setting and whether patients had received TB drugs for more than 7 days was not reported; however, this study accounted for only 7.4% of the total participants in this analysis. We did not downgrade for Indirectness.

Table 4: Should Xpert MTB/RIF be used to diagnose pulmonary TB in sputum in children with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.65 (95% CI: 0.55 to 0.73)
Specificity	0.99 (95% CI: 0.98 to 0.99)

Prevalences	1%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with pulmonary TB)	23 studies 493 patients	cross-sectional (cohort type accuracy study)	not seriou s [a]	serious [b]	not serious [c]	not serious [d]	none	6 (6 to 7)	65 (55 to 73)	129 (111 to 146)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having pulmonary TB)								4 (3 to 4)	35 (27 to 45)	71 (54 to 89)	
True negatives (patients without pulmonary TB)	23 studies 6119 patients	cross-sectional (cohort type accuracy study)	serious [e]	not serious	not serious	not serious	none	980 (971 to 985)	891 (883 to 896)	792 (785 to 796)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having pulmonary TB)								10 (5 to 19)	9 (4 to 17)	8 (4 to 15)	

Explanations

a. As assessed by QUADAS-2, 22 studies (95%) had low risk of bias.

b. Eight studies (34%) had high or unclear concern about applicability because, in these studies, patients were enrolled from inpatient tertiary care centers, which could lead to the enrollment of children with more advanced disease. Of these studies, Nhu 2013 and Singh 2016 had among the highest sensitivities. We downgraded one level for indirectness.

c. For individual studies, sensitivity estimates ranged from 27% to 100%. We thought that differences in enrolment criteria (different populations targeted), disease severity, and different ages and settings could explain the heterogeneity. We did not downgrade for inconsistency.

d. The 95% CI around true positives and false negatives would likely not lead to different decisions depending on which confidence limits are assumed. We did not downgrade for imprecision.

e. As assessed by QUADAS-2, 11 studies (47%) had unclear risk of bias based on the collection of a single culture to exclude tuberculosis. We downgraded one level for risk of bias.

Table 5: Should Xpert Ultra be used to diagnose pulmonary TB in sputum in children with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.73 (95% CI: 0.65 to 0.80)
Specificity	0.97 (95% CI: 0.96 to 0.98)

Prevalences	1%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with pulmonary TB)	3 studies 136 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	7 (6 to 8)	73 (65 to 80)	146 (129 to 159)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having pulmonary TB)								3 (2 to 4)	27 (20 to 35)	54 (41 to 71)	
True negatives (patients without pulmonary TB)	3 studies 551 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	960 (950 to 970)	873 (864 to 882)	776 (768 to 784)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary TB)								30 (20 to 40)	27 (18 to 36)	24 (16 to 32)	

Explanations

a. Two studies (66%) had high concern about applicability because, in these studies, patients were enrolled from inpatient tertiary care centers, which could lead to the enrollment of children with more advanced disease. We downgraded one level.

b. There was a small number of children with pulmonary TB contributing to this analysis for the observed sensitivity. We downgraded one level for imprecision.

Table 6: Should Xpert MTB/RIF be used to diagnose TB meningitis in CSF in adults with signs and symptoms of TB meningitis, against a microbiological reference standard?

Sensitivity	0.70 (95% CI: 0.61 to 0.79)
Specificity	0.97 (95% CI: 0.95 to 0.98)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with TB meningitis)	28 studies 521 patients	cross-sectional (cohort type accuracy study)	not serious [a]	not serious	serious [b]	not serious	none	18 (15 to 20)	70 (61 to 79)	141 (122 to 158)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having TB meningitis)								7 (5 to 10)	30 (21 to 39)	59 (42 to 78)	
True negatives (patients without TB meningitis)	28 studies 2582 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	944 (928 to 956)	871 (857 to 883)	774 (762 to 785)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having TB meningitis)								31 (19 to 47)	29 (17 to 43)	26 (15 to 38)	

Explanations

a. We judged 79% of the studies at low risk of bias. We did not downgrade for risk of bias.

b. The sensitivity ranged from 33% to 100%. We thought that differences in CSF volume and processing could explain in part the heterogeneity, but not all. We downgraded one level for inconsistency.

Table 7: Should Xpert Ultra be used to diagnose TB meningitis in CSF in adults with signs and symptoms of TB meningitis, against a microbiological reference standard?

Sensitivity	0.87 (95% CI: 0.69 to 0.96)
Specificity	0.88 (95% CI: 0.69 to 0.95)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with TB meningitis)	4 studies 40 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	very serious [a]	none	22 (17 to 24)	87 (69 to 96)	174 (139 to 191)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having TB meningitis)								3 (1 to 8)	13 (4 to 31)	26 (9 to 61)	
True negatives (patients without TB meningitis)	4 studies 143 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious [b]	very serious [c]	none	855 (673 to 931)	789 (621 to 859)	702 (552 to 764)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having TB meningitis)								120 (44 to 302)	111 (41 to 279)	98 (36 to 248)	

Explanations

a. There were few participants in this analysis. The very wide 95% CrI around true positives and false negatives may lead to different decisions depending on which credible limits are assumed. We downgraded two levels for imprecision.

b. For individual studies, specificity estimates ranged from 43% (Chin 2019) to 100% (Perez-Risco 2018). Chin 2019 explained that they inoculated uncentrifuged CSF which could have led to low culture positivity, thus resulting in higher number of false positives. Perez-Risco 2018 contributed only 1 participant to this analysis. We did not downgrade for inconsistency.

c. The very wide 95% CrI around true negatives and false positives would likely lead to different decisions depending on which credible limits are assumed. We downgraded two levels for imprecision.

Table 8: Should Xpert MTB/RIF be used to diagnose lymph node TB in lymph node aspirates in adults with signs and symptoms of lymph node TB, against a composite reference standard?

Sensitivity	0.81 (95% CI: 0.62 to 0.92)
Specificity	0.96 (95% CI: 0.90 to 0.98)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with lymph node TB)	4 studies 377 patients	cross-sectional (cohort type accuracy study)	not seriou s	serious [a]	serious [b]	not serious [c]	none	20 (16 to 23)	81 (62 to 92)	162 (124 to 184)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having lymph node TB)								5 (2 to 9)	19 (8 to 38)	38 (16 to 76)	
True negatives (patients without lymph node TB)	4 studies 302 patients	cross-sectional (cohort type accuracy study)	serious [d]	not serious	not serious	serious [e]	none	935 (878 to 958)	863 (811 to 885)	767 (721 to 786)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having lymph node TB)								40 (17 to 97)	37 (15 to 89)	33 (14 to 79)	

Explanations

a. For indirectness, regarding applicability, for the patient selection domain, we considered most studies to have unclear concern. We were interested in how Xpert MTB/RIF performed in patients presumed to have extrapulmonary TB who were evaluated as they would be in routine practice. However, none of the studies reported this information. We downgraded one level for indirectness.

b. For individual studies, sensitivity estimates ranged from 49% to 97%. We could not explain the heterogeneity by study quality or other factors. We downgraded one level for inconsistency.

c. There were few participants contributing to this analysis for the observed sensitivity. As we had already downgraded for inconsistency, we did not downgrade further for imprecision.

d. The composite reference standard was defined by the primary study authors and therefore, was not uniform. We downgraded one level for risk of bias.

e. The very wide 95% CrI for true negatives and false positives may lead to different decisions depending on which credible limits are assumed. We downgraded one level for imprecsion.

Table 9: Should Xpert Ultra be used to diagnose lymph node TB in lymph node aspirates in adults with signs and symptoms of lymph node TB, against a microbiological reference standard?

Sensitivity	0.78 (95% CI: 0.40 to 0.97)
Specificity	0.78 (95% CI: 0.66 to 0.87)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with lymph node TB)	1 studies 9 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	very serious [b]	none	20 (10 to 24)	78 (40 to 97)	156 (80 to 194)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having lymph node TB)								5 (1 to 15)	22 (3 to 60)	44 (6 to 120)	
True negatives (patients without lymph node TB)	1 studies 64 patients	cross-sectional (cohort type accuracy study)	not serious [c]	serious [a]	not serious	very serious [d]	none	761 (644 to 848)	702 (594 to 783)	624 (528 to 696)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having lymph node TB)								214 (127 to 331)	198 (117 to 306)	176 (104 to 272)	

Explanations

a. We identified only one study, which was conducted at a tertiary referral centre in South Africa, a high TB burden country. Although most participants (84%) were seen as outpatients, a high proportion had tuberculosis tests or chest radiographs prior to referral. TB prevalence in the study was 12%. Nonetheless, with only one study, applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

b. There were very few participants contributing to this analysis. The 95% CI was very wide. We downgraded two levels for imprecision.

c. In this study, the lymph node aspirates were not decontaminated before culture inoculation, which is the ideal practice for sterile specimens.

d. There were very few participants contributing to this analysis. The 95% CI was very wide. We downgraded two levels for imprecision.

Table 10: Should Xpert Ultra be used to diagnose lymph node TB in lymph node aspirates in adults with signs and symptoms of lymph node TB, against a composite reference standard?

Sensitivity	0.70 (95% CI: 0.51 to 0.85)
Specificity	1.00 (95% CI: 0.92 to 1.00)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with lymph node TB)	1 studies 30 patients	cross-sectional (cohort type accuracy study)	not seriou s	serious [a]	not serious	very serious [b]	none	17 (13 to 21)	70 (51 to 85)	140 (102 to 170)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having lymph node TB)								8 (4 to 12)	30 (15 to 49)	60 (30 to 98)	
True negatives (patients without lymph node TB)	1 studies 43 patients	cross-sectional (cohort type accuracy study)	not seriou s [c]	serious [a]	not serious	serious [d]	none	975 (897 to 975)	900 (828 to 900)	800 (736 to 800)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having lymph node TB)								0 (0 to 78)	0 (0 to 72)	0 (0 to 64)	

Explanations

a. We identified only one study which was conducted at a referral centre in South Africa, a high TB burden country. Although most participants (84%) were seen as outpatients, a high proportion had tuberculosis tests or chest radiographs prior to referral. TB prevalence in the study was 41%, higher than the TB prevalences provided in the table. In some instances, prevalence may be a marker of disease spectrum, with high prevalence commonly being interpreted as indicative of more severe disease. It is possible the test will perform differently at lower prevalences. Applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

b. There were very few participants contributing to this analysis. The 95% CI was very wide. We downgraded two levels for imprecision.

c. In this study, the lymph node aspirates were not decontaminated before culture inoculation, which is the ideal practice for sterile specimens.

d. There were very few participants contributing to this analysis. In contrast to the 95% CI for sensitivity, for specificity, the interval was relatively narrow. We downgraded one level for imprecision.

Table 11: Should Xpert Ultra be used to diagnose lymph node TB in lymph node biopsies in adults with signs and symptoms of lymph node TB, against a microbiological reference standard?

Sensitivity	0.90 to 1.00
Specificity	0.38 to 0.87

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with lymph node TB)	2 studies 23 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	very serious [c]	none	23 to 25	90 to 100	180 to 200	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having lymph node TB)								0 to 2	0 to 10	0 to 20	
True negatives (patients without lymph node TB)	2 studies 108 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	serious [d]	not serious [e]	none	371 to 848	342 to 783	304 to 696	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having lymph node TB)								127 to 604	117 to 558	104 to 496	

Explanations

a. As assessed by QUADAS-2, we judged risk of bias as unclear because, in one study, the manner of selection not reported. We downgraded one level for risk of bias.

b. There were only two studies in this analysis. One study was conducted at a tertiary referral centre in South Africa; TB prevalence was 12%. The other study was conducted in a tertiary care hospital in China; TB prevalence was 26%. Both studies are high TB burden countries. Applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

c. There were very few participants contributing to this analysis. We downgraded two levels for imprecision.

d. The specificity estimates were variable. We could not explain the variability. We downgraded one level for inconsistency.

e. As we had already downgraded for inconsistency, we did not downgrade further for imprecision.

Table 12: Should Xpert Ultra be used to diagnose lymph node TB in lymph node biopsies in adults with signs and symptoms of lymph node TB, against a composite reference standard?

Sensitivity	0.73 (95% CI: 0.50 to 0.89)
Specificity	0.96 (95% CI: 0.88 to 1.00)

Prevalences	2.5%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with lymph node TB)	1 studies 22 patients	cross-sectional (cohort type accuracy study)	not seriou s	serious [a]	not serious	very serious [b]	none	18 (13 to 22)	73 (50 to 89)	146 (100 to 178)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having lymph node TB)								7 (3 to 12)	27 (11 to 50)	54 (22 to 100)	
True negatives (patients without lymph node TB)	1 studies 57 patients	cross-sectional (cohort type accuracy study)	not seriou s [c]	serious [a]	not serious	very serious [b]	none	936 (858 to 975)	864 (792 to 900)	768 (704 to 800)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having lymph node TB)								39 (0 to 117)	36 (0 to 108)	32 (0 to 96)	

Explanations

a. We identified only one study which was conducted at a referral centre in South Africa, a high TB burden country. Although most participants (84%) were seen as outpatients, a high proportion had tuberculosis tests or chest radiographs prior to referral. TB prevalence in the study was 28%, higher than the TB prevalences provided in the table. Applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

b. There were very few participants contributing to this analysis. The 95% CI was very wide. We downgraded two levels for imprecision.

c. In this study, the lymph node biopsy specimens were not decontaminated before culture inoculation, which is ideal practice for sterile specimens.

Table 13: Should Xpert MTB/RIF be used to diagnose TB meningitis in CSF in children with signs and symptoms of TB meningitis, against a microbiological reference standard?

Sensitivity	0.54 (95% CI: 0.28 to 0.78)
Specificity	0.94 (95% CI: 0.84 to 0.98)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			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 TB meningitis)	6 studies 28 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious [b]	serious [c]	serious [d]	none	5 (3 to 8)	27 (14 to 39)	54 (28 to 78)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having TB meningitis)								5 (2 to 7)	23 (11 to 36)	46 (22 to 72)	
True negatives (patients without TB meningitis)	6 studies 213 patients	cross-sectional (cohort type accuracy study)	serious [e]	not serious	not serious	serious [f]	none	929 (837 to 966)	891 (803 to 927)	844 (761 to 878)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having TB meningitis)								61 (24 to 153)	59 (23 to 147)	56 (22 to 139)	

Explanations

a. As assessed by QUADAS-2, 3 studies (50%) had low risk of bias and the risk of bias was unclear for the remainder. We downgraded one level for risk of bias.
b. The setting was unclear or reflected a tertiary care inpatient setting in 3 studies (50%). However, this is reflective of where the target condition would typically be diagnosed and therefore we did not downgrade for indirectness.
c. For individual studies, sensitivity estimates ranged from 0% to 100%. We thought that differences in enrolment criteria (different populations targeted), disease severity, and setting could only in part explain heterogeneity. We downgraded one for inconsistency.
d. There was a low number of children with TB meningitis contributing to this analysis for the observed sensitivity. We thought the 95% CI around false negatives and true positives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded one level for imprecision.
e. The quality of the reference standard was unclear in 3 studies (50%). We downgraded one level for risk of bias.
f. We thought the 95% CI around false positives and true negatives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded one level for imprecision.

Table 14: Should Xpert Ultra repeated test be used to diagnose pulmonary TB in adults with signs and symptoms of pulmonary TB who have an initial Ultra trace result, against a microbiological reference standard?

Sensitivity	0.69 to 1.00
Specificity	0.47 to 1.00

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary TB)	3 studies 15 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	serious [b]	very serious [c]	none	17 to 25	69 to 100	207 to 300	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having pulmonary TB)								0 to 8	0 to 31	0 to 93	
True negatives (patients without pulmonary TB)	3 studies 25 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [b]	very serious [c]	none	458 to 975	423 to 900	329 to 700	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having pulmonary TB)								0 to 517	0 to 477	0 to 371	

Explanations

a. In Piersimoni 2019, >90% of participants were inpatients in a tertiary care setting. However, this study only contributed four participants (8%) to this analysis. Dorman 2018 was a multi-centre study. We did not downgrade for indirectness.

b. For individual studies, sensitivity estimates ranged from 69% to 100% and specificity from 66% to 100%. The very small number of participants in Mishra 2019a and Piersimoni 2019 (a total of four participants in each study for this analysis) may in part explain the inconsistency. We downgraded one level for inconsistency.

c. Only 3 studies, one of which Dorman 2018 contributed 42 participants and the other 2 studies contributed 4 participants each. We downgraded two levels for imprecision.

Table 15: Should more than one Xpert MTB/RIF vs. one Xpert MTB/RIF be used to diagnose pulmonary TB in sputum in children with signs and symptoms of pulmonary TB, against a microbiological reference standard?

more than one Xpert MTB/RIF		one Xpert MTB/RIF	
Sensitivity	0.59 (95% CI: 0.43 to 0.73)	Sensitivity	0.46 (95% CI: 0.35 to 0.58)
Specificity	0.99 (95% CI: 0.98 to 1.00)	Specificity	1.00 (95% CI: 0.99 to 1.00)

Prevalences	1%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 10%		pre-test probability of 20%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	more than one Xpert MTB/RIF	one Xpert MTB/RIF	more than one Xpert MTB/RIF	one Xpert MTB/RIF	more than one Xpert MTB/RIF	one Xpert MTB/RIF	
True positives (patients with pulmonary TB)	5 studies 180 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	6 (4 to 7)	5 (3 to 6)	59 (43 to 73)	46 (35 to 58)	118 (86 to 146)	92 (70 to 116)	⨁⨁◯◯ LOW
								1 more TP in more than one Xpert MTB/RIF		**13 more TP in more than one Xpert MTB/RIF**		**26 more TP in more than one Xpert MTB/RIF**		
False negatives (patients incorrectly classified as not having pulmonary TB)								4 (3 to 6)	5 (4 to 7)	41 (27 to 57)	54 (42 to 65)	82 (54 to 114)	108 (84 to 130)	
								1 fewer FN in more than one Xpert MTB/RIF		**13 fewer FN in more than one Xpert MTB/RIF**		**26 fewer FN in more than one Xpert MTB/RIF**		
True negatives		cross-sectional	not serious	not serious	not serious	not serious	none	980 (970 to 990)	990 (980 to 990)	891 (882 to 900)	900 (891 to 900)	792 (784 to 800)	800 (792 to 800)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 10%		pre-test probability of 20%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	more than one Xpert MTB/RIF	one Xpert MTB/RIF	more than one Xpert MTB/RIF	one Xpert MTB/RIF	more than one Xpert MTB/RIF	one Xpert MTB/RIF	
(patients without pulmonary TB)	5 studies 1939 patients	(cohort type accuracy study)						**10 fewer TN in more than one Xpert MTB/RIF**		**9 fewer TN in more than one Xpert MTB/RIF**		**8 fewer TN in more than one Xpert MTB/RIF**		⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary TB)								10 (0 to 20)	0 (0 to 10)	9 (0 to 18)	0 (0 to 9)	8 (0 to 16)	0 (0 to 8)	
								10 more FP in more than one Xpert MTB/RIF		**9 more FP in more than one Xpert MTB/RIF**		**8 more FP in more than one Xpert MTB/RIF**		

Explanations

a. Two studies (40%) had high or unclear concern about applicability because, in these studies, patients were enrolled from inpatient tertiary care settings, which could lead to the enrollment of children with more advanced disease. We downgraded one level for indirectness.

b. There was a small number of children with pulmonary TB contributing to this analysis for the observed sensitivity. We thought the 95% CI around false negatives and true positives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded one level for imprecision.

Table 16: Should more than one Xpert Ultra vs. one Xpert Ultra be used to diagnose pulmonary TB in sputum in children with signs and symptoms of pulmonary TB, against a microbiological reference standard?

more than one Xpert Ultra		one Xpert Ultra	
Sensitivity	0.75 (95% CI: 0.55 to 0.89)	Sensitivity	0.64 (95% CI: 0.44 to 0.81)
Specificity	0.98 (95% CI: 0.93 to 0.99)	Specificity	1.00 (95% CI: 0.97 to 1.00)

Prevalences	1%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 10%		pre-test probability of 20%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	more than one Xpert Ultra	one Xpert Ultra	more than one Xpert Ultra	one Xpert Ultra	more than one Xpert Ultra	one Xpert Ultra	
True positives (patients with pulmonary TB)	1 studies 28 patients	cross-sectional (cohort type accuracy study)	not serious	very serious [a]	not serious	very serious [b]	none	8 (6 to 9)	6 (4 to 8)	75 (55 to 89)	64 (44 to 81)	150 (110 to 178)	128 (88 to 162)	⨁◯◯◯ VERY LOW
								2 more TP in more than one Xpert Ultra		**11 more TP in more than one Xpert Ultra**		**22 more TP in more than one Xpert Ultra**		
False negatives (patients incorrectly classified as not having pulmonary TB)								2 (1 to 4)	4 (2 to 6)	25 (11 to 45)	36 (19 to 56)	50 (22 to 90)	72 (38 to 112)	
								2 fewer FN in more than one Xpert Ultra		**11 fewer FN in more than one Xpert Ultra**		**22 fewer FN in more than one Xpert Ultra**		
True negatives (patients without pulmonary TB)	1 studies 135 patients	cross-sectional (cohort type	not serious	very serious [a]	not serious	not serious	none	970 (921 to 980)	990 (960	882 (837 to 891)	900 (873	784 (744 to 792)	800 (776	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 10%		pre-test probability of 20%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	more than one Xpert Ultra	one Xpert Ultra	more than one Xpert Ultra	one Xpert Ultra	more than one Xpert Ultra	one Xpert Ultra	
		accuracy study)							to 990)		to 900)		to 800)	⨁⨁◯◯ LOW
								20 fewer TN in more than one Xpert Ultra		**18 fewer TN in more than one Xpert Ultra**		**16 fewer TN in more than one Xpert Ultra**		
False positives (patients incorrectly classified as having pulmonary TB)								20 (10 to 69)	0 (0 to 30)	18 (9 to 63)	0 (0 to 27)	16 (8 to 56)	0 (0 to 24)	
								20 more FP in more than one Xpert Ultra		**18 more FP in more than one Xpert Ultra**		**16 more FP in more than one Xpert Ultra**		

Explanations

a. Only one study contributed to this analysis. The results may not be applicable to other settings. We downgraded two levels for indirectness.

b. There was a low number of children with pulmonary TB contributing to this analysis for the observed sensitivity. We thought the 95% CI around false negatives and true positives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded two levels for imprecision.

Table 17: Should Xpert MTB/RIF be used to diagnose pulmonary tuberculosis in adults in the general population following a positive TB symptom screen or chest X-ray with lung abnormalities or both, against a microbiological reference standard?

Sensitivity	0.73 (95% CI: 0.62 to 0.82)
Specificity	0.99 (95% CI: 0.98 to 0.99)

Prevalences	1%	3%	7%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 3%	pre-test probability of 7%	
True positives (patients with pulmonary tuberculosis)	4 studies 867 patients	cross-sectional (cohort type accuracy study)	not serious [a]	serious [b]	serious [c]	not serious	none	7 (6 to 8)	22 (19 to 25)	51 (43 to 57)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								3 (2 to 4)	8 (5 to 11)	19 (13 to 27)	
True negatives (patients without pulmonary tuberculosis)	4 studies 48689 patients	cross-sectional (cohort type accuracy study)	not serious [a]	serious [b]	not serious	not serious	none	980 (970 to 980)	960 (951 to 960)	921 (911 to 921)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having pulmonary tuberculosis)								10 (10 to 20)	10 (10 to 19)	9 (9 to 19)	

Explanations

a. The included countries were Bangladesh, Kenya, Philippines, and Viet Nam. Data from Namibia were excluded owing to inconsistencies in the diagnostic algorithm. We did not downgrade for risk of bias. This was a judgement based on an assessment of the quality of the laboratory performing the reference test.

b. The included countries were Bangladesh, Kenya, Philippines, and Viet Nam. The average prevalence of tuberculosis in these countries was 1.7% (range 0.8% to 5.2%), within the range of the pre-test probabilities provided in the table. However, we noted that the populations in these prevalence surveys differed from the general population with respect to prior testing, e.g. symptom screen was limited to cough for 15 days or more, as well as the requirement for results of both symptom screen and chest radiography to be available. We downgraded one level for indirectness.

c. The sensitivity estimate for Bangladesh was 84%, higher than the sensitivity estimates for the other three countries (range, 68% to 69%). We thought we could only explain in part the inconsistency owing to lower HIV prevalence in Bangladesh. We downgraded one level for inconsistency.

Table 18: Should Xpert Ultra be used to diagnose pulmonary tuberculosis in adults in the general population following a positive TB symptom screen or chest X-ray with lung abnormalities or both, against a microbiological reference standard?

Sensitivity	0.68 (95% CI: 0.55 to 0.79)
Specificity	0.98 (95% CI: 0.97 to 0.99)

Prevalences	1%	3%	7%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 3%	pre-test probability of 7%	
True positives (patients with pulmonary tuberculosis)	4 studies 345 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	7 (6 to 8)	20 (17 to 24)	48 (39 to 55)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								3 (2 to 4)	10 (6 to 13)	22 (15 to 31)	
True negatives (patients without pulmonary tuberculosis)	4 studies 12025 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	not serious	none	970 (960 to 980)	951 (941 to 960)	911 (902 to 921)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having pulmonary tuberculosis)								20 (10 to 30)	19 (10 to 29)	19 (9 to 28)	

Explanations

a. The included countries were Myanmar, South Africa, South Africa (TREAT TB project), and Zambia. The average prevalence of tuberculosis in these countries was 2.8% (range 1.6% to 6.7%), within the range of the pre-test probabilities provided in the table. However, we noted that the populations in these prevalence surveys differed from the general population with respect to prior testing, e.g. symptom screen was limited to cough for 15 days or more, as well as the requirement for results of both symptom screen and chest radiography to be available. We downgraded one level for indirectness.

b. There were relatively few participants contributing to this analysis and a wide 95% CI. The 95% CI around true positives and false negatives may lead to different decisions depending on which limits are assumed. We downgraded one level for imprecision.

Table 19: Should two Xpert Ultra vs. one Xpert Ultra be used to diagnose pulmonary tuberculosis in adults in the general population, following a positive TB symptom screen or chest X-ray with lung abnormalities or both, against a microbiological reference standard?

two Xpert Ultra		one Xpert Ultra	
Sensitivity	0.75 (95% CI: 0.59 to 0.87)	Sensitivity	0.64 (95% CI: 0.48 to 0.79)
Specificity	0.97 (95% CI: 0.94 to 0.99)	Specificity	0.98 (95% CI: 0.95 to 0.99)

Prevalences	1%	3%	7%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 3%		pre-test probability of 7%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	two Xpert Ultra	one Xpert Ultra	two Xpert Ultra	one Xpert Ultra	two Xpert Ultra	one Xpert Ultra	
True positives (patients with pulmonary tuberculosis)	3 studies 187 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	very serious [b]	none	8 (6 to 9)	6 (5 to 8)	23 (18 to 26)	19 (14 to 24)	53 (41 to 61)	45 (34 to 55)	⨁◯◯◯ VERY LOW
								2 more TP in two Xpert Ultra		**4 more TP in two Xpert Ultra**		**8 more TP in two Xpert Ultra**		
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								2 (1 to 4)	4 (2 to 5)	7 (4 to 12)	11 (6 to 16)	17 (9 to 29)	25 (15 to 36)	
								2 fewer FN in two Xpert Ultra		**4 fewer FN in two Xpert Ultra**		**8 fewer FN in two Xpert Ultra**		
True negatives (patients without pulmonary tuberculosis)	3 studies 4893 patients	cross-sectional (cohort type	not serious	serious [a]	not serious	not serious	none	960 (931 to 980)	970 (941 to 980)	941 (912 to 960)	951 (922 to 960)	902 (874 to 921)	911 (884 to 921)	⨁⨁⨁◯ MODERATE

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 3%		pre-test probability of 7%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	two Xpert Ultra	one Xpert Ultra	two Xpert Ultra	one Xpert Ultra	two Xpert Ultra	one Xpert Ultra	
		accuracy study)						**10 fewer TN in two Xpert Ultra**		**10 fewer TN in two Xpert Ultra**		**9 fewer TN in two Xpert Ultra**		
False positives (patients incorrectly classified as having pulmonary tuberculosis)								30 (10 to 59)	20 (10 to 49)	29 (10 to 58)	19 (10 to 48)	28 (9 to 56)	19 (9 to 46)	
								10 more FP in two Xpert Ultra		**10 more FP in two Xpert Ultra**		**9 more FP in two Xpert Ultra**		

Explanations

a. Three countries, Myanmar, Zambia, and South Africa, contributed data to this analysis. Myanmar contributed most data. Data may not be applicable to other settings. We downgraded one level for indirectness.

b. There were few participants contributing data to this analysis. The 95% CIs for two Xpert Ultra and one Xpert Ultra were wide. We downgraded two levels for imprecision.

2.2 GRADE profiles: Truenat MTB, MTB Plus and MTB-Rif Dx

Table 20: Should Truenat MTB be used to diagnose pulmonary tuberculosis in adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.73 (95% CI: 0.68 to 0.78)
Specificity	0.98 (95% CI: 0.97 to 0.99)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	1 studies 258 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	serious [b]	none	18 (17 to 20)	73 (68 to 78)	220 (203 to 235)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								7 (5 to 8)	27 (22 to 32)	80 (65 to 97)	
True negatives (patients without pulmonary tuberculosis)	1 studies 1078 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	955 (945 to 961)	881 (872 to 887)	685 (678 to 690)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having pulmonary tuberculosis)								20 (14 to 30)	19 (13 to 28)	15 (10 to 22)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to these analyses. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB. Prevalence of tuberculosis ranged from 12.3% (Ethiopia) to 24.7% (Peru), within the range presented in the pre-test probability table.

b. The 95% CI around true positives and false negatives would probably not lead to different decisions depending on which limits are assumed. However, there were relatively few participants contributing to this analysis. We downgraded one level for imprecision.

Table 21: Should Truenat MTB be used to diagnose pulmonary tuberculosis in smear-positive adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.91 (95% CI: 0.86 to 0.94)
Specificity	-- (95% CI: -- to --)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	1 studies 174 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	serious [b]	none	23 (21 to 24)	91 (86 to 94)	272 (257 to 283)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								2 (1 to 4)	9 (6 to 14)	28 (17 to 43)	
True negatives (patients without pulmonary tuberculosis)	0 studies patients							0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	-
False positives (patients incorrectly classified as having pulmonary tuberculosis)								975 (975 to 975)	900 (900 to 900)	700 (700 to 700)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to this analysis. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB.

b. The 95% around true positives and false negatives would probably not lead to different decisions depending on which limits are assumed. However, there were relatively few participants contributing to this analysis. We downgraded one level for imprecision.

Table 22: Should Truenat MTB be used to diagnose pulmonary tuberculosis in smear-negative adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.37 (95% CI: 0.27 to 0.48)
Specificity	0.98 (95% CI: 0.97 to 0.99)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	1 studies 84 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	serious [b]	serious [c]	none	9 (7 to 12)	37 (27 to 48)	111 (82 to 143)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								16 (13 to 18)	63 (52 to 73)	189 (157 to 218)	
True negatives (patients without pulmonary tuberculosis)	1 studies 1078 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	955 (944 to 961)	881 (871 to 887)	685 (678 to 690)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having								20 (14 to 31)	19 (13 to 29)	15 (10 to 22)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
pulmonary tuberculosis)											

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to these analyses. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB.

b. Sensitivity estimates were variable, 21.1% (India), 47.4% (Peru), and 62.5% (Ethiopia), although the 95% CIs overlapped. We thought differences in patient spectrum (e.g. greater proportion of paucibacillary patients) might in part explain the lower sensitivity estimate in India. We downgraded one level for inconsistency.

c. There were few participants contributing to this analysis. As we had already downgraded one level for inconsistency, we downgraded one level for imprecision.

Table 23: Should Truenat MTB Plus be used to diagnose pulmonary tuberculosis in adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.80 (95% CI: 0.75 to 0.84)
Specificity	0.97 (95% CI: 0.95 to 0.97)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	1 studies 258 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	serious [b]	none	20 (19 to 21)	80 (75 to 84)	239 (224 to 253)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								5 (4 to 6)	20 (16 to 25)	61 (47 to 76)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True negatives (patients without pulmonary tuberculosis)	1 studies 1078 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	941 (928 to 950)	868 (857 to 877)	676 (666 to 682)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary tuberculosis)								34 (25 to 47)	32 (23 to 43)	24 (18 to 34)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to the analyses. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB. Prevalence of tuberculosis ranged from 12.3% (Ethiopia) to 24.7% (Peru), within the range presented in the pre-test probability table.

b. The 95% CI around true positives and false negatives would probably not lead to different decisions depending on which limits are assumed. However, there were relatively few participants contributing to this analysis. We downgraded one level for imprecision.

Table 24: Should Truenat MTB Plus be used to diagnose pulmonary tuberculosis in smear-positive adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.96 (95% CI: 0.92 to 0.98)
Specificity	-- (95% CI: -- to --)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with		cross-sectional (cohort type	not serious	not serious [a]	not serious	serious [b]	none	24 (23 to 25)	96 (92 to 98)	288 (276 to 294)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
pulmonary tuberculosis)	1 studies 174 patients	accurac y study)									⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								1 (0 to 2)	4 (2 to 8)	12 (6 to 24)	
True negatives (patients without pulmonary tuberculosis)	0 studies patients	cross-sectional (cohort type accuracy study)						0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	-
False positives (patients incorrectly classified as having pulmonary tuberculosis)								975 (975 to 975)	900 (900 to 900)	700 (700 to 700)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to this analysis. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB.

b. The 95% CI around the pooled sensitivity estimate is narrow. However, there were relatively few participants contributing to this analysis. We downgraded one level for imprecision.

Table 25: Should Truenat MTB Plus be used to diagnose pulmonary tuberculosis in smear-negative adults with signs and symptoms of pulmonary TB, against a microbiological reference standard?

Sensitivity	0.46 (95% CI: 0.36 to 0.57)
Specificity	0.97 (95% CI: 0.95 to 0.97)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with pulmonary tuberculosis)	1 studies 84 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	serious [b]	serious [c]	none	12 (9 to 14)	46 (36 to 57)	139 (108 to 171)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having pulmonary tuberculosis)								13 (11 to 16)	54 (43 to 64)	161 (129 to 192)	
True negatives (patients without pulmonary tuberculosis)	1 studies 1078 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	941 (928 to 950)	868 (857 to 877)	676 (666 to 682)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having pulmonary tuberculosis)								34 (25 to 47)	32 (23 to 43)	24 (18 to 34)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. The site in Papua New Guinea did not have a microscopy centre and thus did not contribute data to these analyses. India and Ethiopia are included in the WHO high-burden country lists for TB, TB/HIV, and MDR-TB and Peru in the high-burden country list for MDR-TB.

b. Sensitivity estimates were variable, 30.8% (India), 57.9% (Peru), and 62.5% (Ethiopia), although the 95% CIs overlapped. We thought differences in patient spectrum (e.g. greater proportion of paucibacillary patients) might in part explain the lower sensitivity estimate in India. We downgraded one level for inconsistency.

c. There were few participants contributing to this analysis. The 95% CI around true positives and false negatives may lead to different decisions depending on which limits are assumed. As we had already downgraded one level for inconsistency, we downgraded one level for imprecision.

Table 26: Should Truenat MTB-RIF Dx be used to diagnose rifampicin resistance in adults with signs and symptoms of pulmonary TB, microscopy centres?

Sensitivity	0.84 (95% CI: 0.62 to 0.95)
Specificity	0.95 (95% CI: 0.91 to 0.98)

Prevalences	2%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with rifampicin resistance)	1 studies 19 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	serious [b]	very serious [c]	none	17 (12 to 19)	84 (62 to 95)	126 (94 to 142)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having rifampicin resistance)								3 (1 to 8)	16 (5 to 38)	24 (8 to 56)	
True negatives (patients without rifampicin resistance)	1 studies 167 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [d]	none	933 (889 to 956)	857 (816 to 878)	809 (771 to 830)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having rifampicin resistance)								47 (24 to 91)	43 (22 to 84)	41 (20 to 79)	

Explanations

a. This was a multi-centre study taking place in India, Peru, Ethiopia, and Papua New Guinea. Data are from microscopy centres. Papua New Guinea (reference center) did not contribute data to this analysis. India, Peru, and Ethiopia are included in the WHO high-burden country list for MDR-TB. India and Peru contributed most of the data to the determination of rifampicin resistance (in the table, true positives and false negatives) because Ethiopia contributed only one participant with rifampicin resistance. The distribution of rifampicin resistance mutations detected by the assay is unknown. These results may not be applicable to other settings. We downgraded one level for Indirectness.

b. Sensitivity estimates were variable: 100% for Peru (based on 8 RIF-resistant specimens),100% for Ethiopia (based on 1 RIF-resistant specimen), and 70% for India (based on 10 RIF-resistant specimens). We downgraded one level for inconsistency.

c. When reflexed to Truenat MTB-RIF Dx from a positive result on either Truenat MTB or Truenat MTB Plus, the proportion of non-determinate Truenat MTB-RIF Dx results was 8.8% and 15.9%, respectively. There were very few participants contributing to this analysis. The 95% CI around true positives and false negatives may lead to different decisions depending on which limits are assumed. We downgraded two levels for imprecision.

d. When reflexed to Truenat MTB-RIF Dx from a positive result on either Truenat MTB or Truenat MTB Plus, the proportion of non-determinate Truenat MTB-RIF Dx results was 8.8% and 15.9%, respectively. The 95% CI around true negatives and false positives may lead to different decisions depending on which limits are assumed. We downgraded one level for imprecision.

2.3 GRADE profiles: Moderate complexity automated NAATs

Table 27: Should Moderate complexity automated NAATs on respiratory specimens be used to diagnose PTB in adults (> 15 years) with signs and symptoms ofTB, MRS?

Sensitivity	0.93 (95% CI: 0.91 to 0.95)
Specificity	0.98 (95% CI: 0.96 to 0.99)

Prevalences	2.5%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.5%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with PTB)	29 studies 4767 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious [b]	not serious	not serious	none	23 (23 to 24)	93 (91 to 95)	279 (273 to 284)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having PTB)								2 (1 to 2)	7 (5 to 9)	21 (16 to 27)	
True negatives (patients without PTB)	29 studies 9085 patients	cross-sectional (cohort type accuracy study)	not seriou s	not serious [b]	not serious	not serious	none	953 (932 to 963)	879 (860 to 889)	684 (669 to 692)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having PTB)								22 (12 to 43)	21 (11 to 40)	16 (8 to 31)	

Explanations

a. Of the total 29 studies, 16 (55%) had high or unclear risk of bias as they either did prior testing before including specimens in the study or used convenience sampling or the method of participant selection was not reported. We downgraded one level for risk of bias.

b. Median TB prevalence in these studies was 31% and the number of specimens for TB positive and TB negative are large, so we decided to not downgrade for indirectness.

Table 28: Should Moderate complexity automated NAATs on respiratory specimens be used to diagnose rifampicin resistance in adults (> 15 years) with microbiologically confirmed PTB, MRS?

Sensitivity	0.97 (95% CI: 0.93 to 0.98)
Specificity	0.99 (95% CI: 0.97 to 0.99)

Prevalences	2%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with rifampicin resistance)	18 studies 702 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious [b]	not serious	not serious	none	19 (19 to 20)	97 (93 to 98)	145 (140 to 148)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having rifampicin resistance)								1 (0 to 1)	3 (2 to 7)	5 (2 to 10)	
True negatives (patients without rifampicin resistance)	18 studies 2172 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	969 (956 to 975)	890 (878 to 896)	841 (829 to 846)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having rifampicin resistance)								11 (5 to 24)	10 (4 to 22)	9 (4 to 21)	

Explanations

a. There were 8 (44%) out of 18 studies that had high or unclear risk of bias as the participant selection was not reported or there was prior testing done for the specimens included in the study. We downgraded one level for risk of bias.

b. The median prevalence of rifampicin resistance in these studies was 15%, which is representative of drug resistance in most countries for pulmonary TB. We did not downgrade for indirectness.

Table 29: Should Moderate complexity automated NAATs on respiratory specimens be used to diagnose isoniazid resistance in adults (> 15 years) with microbiologically confirmed PTB, MRS?

Prevalences	2%	10%	15%

Sensitivity	0.86 (95% CI: 0.83 to 0.89)
Specificity	0.99 (95% CI: 0.98 to 1.00)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with isoniazid resistance)	18 studies 854 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious [b]	not serious [c]	not serious	none	17 (17 to 18)	86 (83 to 89)	130 (124 to 134)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having isoniazid resistance)								3 (2 to 3)	14 (11 to 17)	20 (16 to 26)	
True negatives (patients without isoniazid resistance)	18 studies 1904 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [b]	not serious	not serious	none	972 (961 to 977)	893 (883 to 897)	843 (834 to 847)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having isoniazid resistance)								8 (3 to 19)	7 (3 to 17)	7 (3 to 16)	

Explanations

a. There were 8 (44%) out of 18 studies that had high or unclear risk of bias as the participant selection was not reported or there was prior testing done for the specimens included in the study. We downgraded one level for risk of bias.

b. The median prevalence in these studies was 19.7%. With high number of specimens being evaluated in these studies, we did not downgrade for indirectness.

c. Sensitivity for INH resistance ranges from 58% to 100%. There was one study with low sensitivity, however, overlapping confidence intervals were seen. We did not downgrade for inconsistency.

2.4 GRADE profiles: Lateral flow urine lipoarabinomannan assay (LF-LAM)

Table 30. AlereLAM compared to no AlereLAM in HIV-positive adults to reduce mortality associated with advanced HIV disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AlereLAM	no AlereLAM	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	496/2544 (19.5%)	589/2558 (23.0%)	**RR 0.85** (0.76 to 0.94)	**35 fewer per 1,000** (from 55 fewer to 14 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Explanations

a. In Gupta-Wright 2018, investigators, all study staff (other than the laboratory technician and statistician), hospital attending clinical teams, and patients were masked to the study group allocation. In Peter 2016, neither patients nor research nurses were masked to either allocation or test results. However, we doubt that the test results were biased in light of this. We did not downgrade.

b. The two trials were conducted in African countries and we do not have direct evidence of the applicability of the findings to other settings outside of Africa. We downgraded one level for indirectness.

Table 31. AlereLAM compared to no AlereLAM in HIV-positive adults to reduce mortality associated with advanced HIV disease, inpatient setting, CD4 ≤ 200

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AlereLAM	no AlereLAM	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 56 weeks)												
2	randomised trials	not serious [a]	not serious	serious [b]	not serious	none	359/1449 (24.8%)	409/1437 (28.5%)	**RR 0.87** (0.77 to 0.99)	**37 fewer per 1,000** (from 65 fewer to 3 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Explanations

a. In Gupta-Wright 2018a, investigators, all study staff (other than the laboratory technician and statistician), hospital attending clinical teams, and patients were masked to the study group allocation. In Peter 2016, neither patients nor research nurses were masked to either allocation or test results. However, we doubt that the test results were biased in light of this. We did not downgrade for risk of bias.

b. The two trials were conducted in African countries and we do not have direct evidence of the applicability of the findings to other settings outside of Africa. In Gupta-Wright et al, the test was conducted in the laboratory, not at the point of care. In addition, in Gupta-Wright, the intervention was a combination of urine LAM and urine Xpert. In Peter et al, the intervention was urine LAM plus a 'nurse-informed' treatment decision. These additional considerations may not reflect how the test will be performed in routine practice. We downgraded one level for indirectness.

Table 32: Should AlereLAM be used to diagnose active TB in HIV-positive adults with TB symptoms, outpatient settings?

Sensitivity	0.29 (95% CI: 0.17 to 0.47)
Specificity	0.96 (95% CI: 0.91 to 0.99)

Prevalences	1%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with active TB)	4 studies 409 patients	cross-sectional (cohort type accuracy study)	very serious [a]	not serious [b]	not serious	not serious [c]	none	3 (2 to 5)	29 (17 to 47)	87 (51 to 141)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having active TB)								7 (5 to 8)	71 (53 to 83)	213 (159 to 249)	
True negatives (patients without active TB)	4 studies 787 patients	cross-sectional (cohort type accuracy study)	serious [d]	not serious [b]	not serious	serious [e]	none	950 (901 to 980)	864 (819 to 891)	672 (637 to 693)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having active TB)								40 (10 to 89)	36 (9 to 81)	28 (7 to 63)	

Explanations

a. As assessed by QUADAS-2, in the patient selection domain, we judged all studies at high risk of bias because they did not avoid inappropriate exclusions. We downgraded two levels for risk of bias.

b. The median TB prevalence in the studies was 43% and thus the results tend to be more applicable to settings with a higher TB prevalence. We did not downgrade for indirectness.

c. The 95% CrI around true positives and false negatives would likely not lead to different decisions depending on which credible limits are assumed. We did not downgrade for imprecision.

d. As assessed by QUADAS-2, in the reference standard domain, we judged three studies (75%) at high risk of bias because we thought the reference standard used was unlikely to correctly classify the target condition. We downgraded one level for risk of bias.

e. The 95% CrI around true negatives and false positives may lead to different decisions depending on which credible limits are assumed. We downgraded one level for imprecision.

Table 33: Should AlereLAM be used to diagnose active TB in HIV-positive adults irrespective of symptoms, outpatient settings, CD4 ≤ 100?

Sensitivity	0.40 (95% CI: 0.20 to 0.64)
Specificity	0.87 (95% CI: 0.68 to 0.94)

Prevalences	1%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with active TB)	2 studies 46 patients	cross-sectional (cohort type accuracy study)	very serious [a]	not serious	not serious	very serious [b]	none	4 (2 to 6)	40 (20 to 64)	120 (60 to 192)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having active TB)								6 (4 to 8)	60 (36 to 80)	180 (108 to 240)	
True negatives (patients without active TB)	2 studies 171 patients	cross-sectional (cohort type accuracy study)	very serious [c]	not serious	not serious	very serious [d]	none	861 (673 to 931)	783 (612 to 846)	609 (476 to 658)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having active TB)								129 (59 to 317)	117 (54 to 288)	91 (42 to 224)	

Explanations

a. As assessed by QUADAS-2, in the patient selection domain, we considered both studies at high risk of bias because they did not avoid inappropriate exclusions. We downgraded two levels for risk of bias.

b. There were few participants in this analysis. We downgraded two levels for imprecision.

c. As assessed by QUADAS-2, in the reference standard domain, we considered both studies at high risk of bias because we thought the reference standard used was unlikely to correctly classify the target condition. We downgraded two levels for risk of bias.

d. The very wide 95% CrIs around true negatives and false positives may lead to different decisions depending on which credible limits are assumed. We downgraded two levels for imprecision.

Table 34. Should AlereLAM be used to diagnose active TB in HIV-positive adults irrespective of symptoms, outpatient settings?

Sensitivity	0.31 (95% CI: 0.18 to 0.47)
Specificity	0.95 (95% CI: 0.87 to 0.99)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			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)	6 studies 273 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious [b]	not serious [c]	none	3 (2 to 5)	16 (9 to 24)	31 (18 to 47)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having active TB)								7 (5 to 8)	34 (26 to 41)	69 (53 to 82)	
True negatives (patients without active TB)	6 studies 2555 patients	cross-sectional (cohort type accuracy study)	very serious [d]	not serious	not serious [e]	serious [f]	none	941 (861 to 980)	903 (827 to 941)	855 (783 to 891)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having active TB)								49 (10 to 129)	47 (9 to 123)	45 (9 to 117)	

Explanations

a. As assessed by QUADAS-2, in the patient selection domain, we judged four studies (67%) at high risk of bias because they did not avoid inappropriate exclusions. We downgraded one level for risk of bias.
b. For individual studies, sensitivity ranged from 0% to 63%. We thought that the percentage of patients with TB symptoms or CD4 count could explain in part the heterogeneity. One study (LaCourse 2016) with sensitivity 0% differed from the other studies by including a) a population of exclusively pregnant women attending an antenatal care setting, b) a low proportion of symptomatic participants (19%), c) a low TB prevalence (1%), and d) a high median CD4 cell count (437 cells per µL). One study (Thit 2017) with sensitivity 63% differed from the other studies by being conducted in Myanmar, and is the only study included in this review that evaluated AlereLAM in a setting outside sub-Saharan Africa. We did not downgrade for inconsistency.
c. We thought the wide 95% CrIs around true positives and false negatives would likely not lead to different decisions depending on which credible limits are assumed. We did not downgrade for imprecision.
d. As assessed by QUADAS-2, in the reference standard domain, we judged five studies (83%) at high risk of bias because we thought the reference standard used was unlikely to correctly classify the target condition. We downgraded two levels for risk of bias.
e. For individual studies, specificity ranged from 67% to 99%. Five of the studies had specificity of 94% or higher. One study (Thit 2017) with specificity 67% differed from the other studies by being conducted in Myanmar, and is the only study included in this review that evaluated AlereLAM in a setting outside sub-Saharan Africa. We did not downgrade further for inconsistency.
f. The wide 95% CrIs around true negatives and false positives may lead to different decisions depending on which credible limits are assumed. We downgraded one level for imprecision.

Table 35: Should AlereLAM be used to diagnose active TB in HIV-positive adults no symptoms and no CD4 count available?

Sensitivity	0.21 (95% CI: 0.08 to 0.48)
Specificity	0.96 (95% CI: 0.89 to 0.99)

Prevalences	1%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with active TB)	0 studies patients							2 (1 to 5)	21 (8 to 48)	63 (24 to 144)	-
False negatives (patients incorrectly classified as not having active TB)								8 (5 to 9)	79 (52 to 92)	237 (156 to 276)	
True negatives (patients without active TB)	0 studies patients							950 (881 to 980)	864 (801 to 891)	672 (623 to 693)	-
False positives (patients incorrectly classified as having active TB)								40 (10 to 109)	36 (9 to 99)	28 (7 to 77)	

Table 36: Should AlereLAM be used to diagnose active TB in HIV-positive adults irrespective of symptoms, outpatient settings, CD4 ≤ 200?

Sensitivity	0.21 (95% CI: 0.08 to 0.48)
Specificity	0.96 (95% CI: 0.89 to 0.99)

Prevalences	1%	10%	30%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 30%	
True positives (patients with active TB)	2 studies 65 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious [b]	very serious [c]	none	2 (1 to 5)	21 (8 to 48)	63 (24 to 144)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having active TB)								8 (5 to 9)	79 (52 to 92)	237 (156 to 276)	
True negatives (patients without active TB)	2 studies 587 patients	cross-sectional (cohort type accuracy study)	serious [d]	not serious	not serious	serious [e]	none	950 (881 to 980)	864 (801 to 891)	672 (623 to 693)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having active TB)								40 (10 to 109)	36 (9 to 99)	28 (7 to 77)	

Explanations

a. As assessed by QUADAS-2, in the patient selection domain, we judged one study (50%) at high risk of bias because this study did not avoid inappropriate exclusions. We downgraded one level for risk of bias.

b. We thought that differences in the percentage of patients with TB symptoms in the two studies could explain some of the heterogeneity. We did not downgrade for inconsistency.

c. The wide 95% CrI around true positives and false negatives would likely not lead to different decisions depending on which credible limits are assumed. However, there were few participants in this analysis. We downgraded two levels for imprecision.

d. As assessed by QUADAS-2, in the reference standard domain, we judged one study (50%) at high risk of bias because we thought the reference standard used was unlikely to correctly classify the target condition. We downgraded one level for risk of bias.

e. The wide 95% CrIs around true negatives and false positives would likely lead to different decisions depending on which credible limits are assumed. We downgraded one level for imprecision.

2.5 GRADE profiles: Low complexity automated NAATs

Table 37: Should Low complexity automated NAATs on sputum be used to diagnose INH resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to RIF, MRS?

Sensitivity	0.94 (95% CI: 0.89 to 0.97)
Specificity	0.98 (95% CI: 0.95 to 0.99)

Prevalences	2%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with INH resistance)	3 studies 994 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious [b]	not serious	none	19 (18 to 19)	94 (89 to 97)	141 (134 to 146)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having INH resistance)								1 (1 to 2)	6 (3 to 11)	9 (4 to 16)	
True negatives (patients without INH resistance)	3 studies 611 patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	not serious	none	960 (933 to 972)	882 (857 to 893)	833 (809 to 843)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having INH resistance)								20 (8 to 47)	18 (7 to 43)	17 (7 to 41)	

Explanations

a. We had several concerns about whether there is indirectness in the populations studied. First, the median prevalence of isoniazid resistance in the included studies was 67.2% (range, 26.8% (DIAMA, Benin) to 93.9% (FIND, Moldova), higher than the three prevalences in the GRADE table. Applicability to settings with a lower prevalence of isoniazid resistance comes with some uncertainty. Second, there are potential differences in the mutations

present in isoniazid mono-resistant strains and MDR strains. That is, there are studies that suggest that a more diverse set of mutations can be found in mono-resistant strains that MDR strains. Third, although the population for this PICO question is 'irrespective of rifampicin resistance,' owing to enrollment criteria in the studies, we note that most participants were rifampicin resistant. We downgraded one level for indirectness.

b. Sensitivity estimates ranged from 81% (FIND, New Delhi) to 100% (DIAMA, Rwanda). Regarding the low sensitivity estimate in New Delhi, the study authors reported that sequencing did not show the presence of variants typically associated with resistance in many phenotypically isoniazid-resistant samples suggesting that variants not analyzed by Xpert MTB/XDR might play a role. We did not downgrade for inconsistency. This was a judgement.

Table 38: Should Low complexity automated NAATs on sputum be used to diagnose FQ resistance in patients with microbiologically confirmed pulmonary TB, irrespective of resistance to RIF, MRS?

Sensitivity	0.93 (95% CI: 0.88 to 0.96)
Specificity	0.98 (95% CI: 0.94 to 0.99)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			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 FQ resistance)	3 studies 384 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious [b]	not serious	none	9 (9 to 10)	47 (44 to 48)	93 (88 to 96)	⨁⨁⨁⨁ HIGH
False negatives (patients incorrectly classified as not having FQ resistance)								1 (0 to 1)	3 (2 to 6)	7 (4 to 12)	
True negatives (patients without FQ resistance)	3 studies 953 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	serious [c]	not serious	none	973 (936 to 985)	934 (898 to 945)	885 (850 to 896)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having FQ resistance)								17 (5 to 54)	16 (5 to 52)	15 (4 to 50)	

Explanations

a. The median prevalence of fluoroquinolone resistance in the included studies was 24.3% (range, 0.0% (DIAMA, Rwanda) to 58.4% (FIND, Mumbai), higher than the three prevalences listed in the GRADE table. Applicability to settings with lower prevalence of fluoroquinolone resistance comes with some uncertainty. Although the population for this PICO question is 'irrespective of rifampicin resistance,' owing to enrollment criteria in the studies, we note that most participants were rifampicin resistant. We did not downgrade for indirectness.

b. Sensitivity estimates ranged from 83% (FIND, New Delhi) to 100% (DIAMA, Benin and Cameroon). Except for New Delhi, sensitivity was > 90%. We did not downgrade for inconsistency.

c. Specificity estimates were inconsistent: 84% (FIND, Mumbai), 91% (FIND, New Delhi), and > 96% for other studies. We could not explain the heterogeneity in specificity estimates. We downgraded one level inconsistency.

Table 39: Should Low complexity automated NAATs on sputum be used to diagnose ETO resistance in patients with microbiologically confirmed pulmonary TB, with detected resistance to RIF, gDST?

Sensitivity	0.98 (95% CI: 0.74 to 1.00)
Specificity	1.00 (95% CI: 0.83 to 1.00)

Prevalences	20%	30%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 30%	pre-test probability of 50%	
True positives (patients with ETO resistance)	1 studies 167 patients	cross-sectional (cohort type accuracy study)	very serious [a]	not serious [b]	not serious [c]	serious [d]	none	196 (148 to 200)	294 (223 to 300)	490 (371 to 500)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having ETO resistance)								4 (0 to 52)	6 (0 to 77)	10 (0 to 129)	
True negatives (patients without ETO resistance)	1 studies 267 patients	cross-sectional (cohort type accuracy study)	very serious [a]	not serious [b]	not serious	serious [e]	none	798 (668 to 800)	698 (584 to 700)	499 (418 to 500)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having ETO resistance)								2 (0 to 132)	2 (0 to 116)	1 (0 to 82)	

Explanations

a. We thought there was very serious risk of bias in the reference standard domain because the study did not include all of the loci (i.e. ethA, ethR, and inhA promoter) required for the reference standard to correctly classify the target condition. Of note, against a reference standard of pDST, the pooled sensitivity estimate was considerably lower at 51.7% (33.1 to 69.8). We downgraded two levels for risk of bias.

b. The median prevalence of ethionamide resistance in the included studies was 39.3%, range, 13.6% (FIND, New Delhi) to 61.5% (FIND, South Africa), higher than the three prevalences listed in the GRADE table. Applicability to settings with lower prevalence of ethionamide resistance comes with some uncertainty. We did not downgrade for indirectness.

c. Sensitivity estimates ranged from 78% (FIND, Moldova) to 100% (FIND, Moldova and Mumbai). The heterogeneity could in part explained by small numbers of resistant cases in Moldova and South Africa. We did not downgrade for inconsistency.

d. The 95% CI was wide. We thought the 95% CI around true positives and false negatives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded one level for imprecision.

e. We thought the 95% CI around true negatives and false positives would likely lead to different decisions depending on which confidence limits are assumed. We downgraded one level for imprecision.

Table 40: Should Low complexity automated NAATs on sputum be used to diagnose AMK resistance in patients with microbiologically confirmed pulmonary TB, with detected resistance to RIF, MRS?

Sensitivity	0.86 (95% CI: 0.75 to 0.93)
Specificity	0.99 (95% CI: 0.93 to 1.00)

Prevalences	6%	13.5%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 6%	pre-test probability of 13.5%	pre-test probability of 20%	
True positives (patients with AMK resistance)	1 studies 65 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious [b]	very serious [c]	none	52 (45 to 56)	116 (101 to 125)	172 (150 to 185)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having AMK resistance)								8 (4 to 15)	19 (10 to 34)	28 (15 to 50)	
True negatives (patients without AMK resistance)	1 studies 425 patients	cross-sectional (cohort type accuracy study)	not serious	not serious [a]	not serious	not serious	none	930 (874 to 938)	855 (804 to 863)	791 (744 to 798)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having AMK resistance)								10 (2 to 66)	10 (2 to 61)	9 (2 to 56)	

Explanations

a. The median prevalence of amikacin resistance in the FIND multi-centre study was 13.5%, range 5.7% (Moldova) to 36.1% (South Africa). Based on this information and input from the GDG members, we used prevalences of 6.0%, 13.5%, and 20% in the GRADE table.

b. Sensitivity estimates were somewhat inconsistent, ranging from 75% (FIND, New Delhi) to 95% (FIND, South Africa). Regarding the finding of low amikacin sensitivity estimates in the FIND study, the authors provided the following explanation. "This issue appears to be linked exclusively to samples with rrs c1402a and g1484t double mutations (12 in New Delhi, 3 in Moldova). The g1484t mutation was considered to be a marker of phenotypic amikacin resistance in the FIND analysis, but 14/15 of these mutated samples were pDST AMK-S (1 was pDST contaminated). Importantly, all of these pDST AMK-S/WGS AMK-R samples with the mutations noted above tested susceptible by Hain LPA as well as Xpert XDR, so we have more confidence in the Xpert (rather than WGS) result." We also note New Delhi had a small number of resistant cases. These explanations may in part explain the heterogeneity in sensitivity estimates. We did not downgrade for inconsistency. This was a judgement.

c. The 95% CI was wide. We thought the 95% CI around true positives and false negatives would likely lead to different decisions depending on which confidence limits are assumed. Also, there was a very low number of participants with amikacin resistance contributing to this analysis for the observed sensitivity. We downgraded two levels for imprecision.

2.6 GRADE profiles: First-line line probe assay (FL-LPA)

Table 41. Accuracy of line probe assays (LPAs) by direct testing for detecting rifampicin resistance in patients with signs and symptoms of TB

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan). The tests were performed by direct testing on smear-positive specimens.

Reference standard: Culture-based drug-susceptibility testing
Studies: Case–control or cohort studies comparing LPAs with a reference standard

Sensitivity	0.96 (95% CI: 0.95–0.97)
Specificity	0.98 (95% CI: 0.97–0.99)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)		Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	
True positives (patients with rifampicin resistance)	48 studies (2 876 patients)	Cohort and case–control-type studies	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None	48 (47–49)	144 (142–146)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having rifampicin resistance)								2 (1–3)	6 (4–8)	
True negatives (patients without rifampicin resistance)	48 studies (7 684 patients)	Cohort and case–	Serious[a]	Not serious[b]	Not serious[c]	Not serious[e]	None	933 (923–939)	835 (826–840)	⊕⊕⊕◯ MODERATE

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)		Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	
False positives (patients incorrectly classified as having rifampicin resistance)		control-type studies						17 (11–27)	15 (10–24)	

[a] The QUADAS-2 tool was used to assess the risk of bias. The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (33/48 studies), because the method of patient sampling was unspecified (for example, consecutive or random). There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (30/48 and 32/48, respectively). The risk of bias was low for the flow and timing domain. The evidence was downgraded by one point.

[b] There was low concern about applicability. Given the tests' high specificity and ability to provide results within a matter of days, the tests might improve patients' outcomes by enabling earlier initiation of appropriate therapy. The evidence was not downgraded.

[c] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies.

[d] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction.

Table 42. Accuracy of LPAs for detecting rifampicin resistance by indirect testing of *Mycobacterium tuberculosis* complex culture isolates

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan). The tests were performed by indirect testing on culture isolates.

Reference standard: Culture-based drug-susceptibility testing
Studies: Case–control or cohort studies comparing LPAs with a culture-based drug-susceptibility reference test

Sensitivity	0.97 (95% CI: 0.95–0.98)
Specificity	0.99 (95% CI: 0.99–1.00)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)		Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	
True positives (patients with rifampicin resistance)	43 studies (3 913 patients)	Cohort and case–control-type studies	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None	48 (48–49)	145 (143–147)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having rifampicin resistance)								2 (1–2)	5 (3–7)	
True negatives (patients without rifampicin resistance)	43 studies (6 783 patients)	Cohort and case–control-type studies	Serious[a]	Not serious[b]	Not serious[c]	Not serious[e]	None	943 (937–946)	844 (838–847)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having rifampicin resistance)								7 (4–13)	6 (3–12)	

[a] The QUADAS-2 tool was used to assess the risk of bias. The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (23/43 studies), because the method of patient sampling was unspecified (for example, consecutive or random). There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (36/43 and 36/43, respectively). The risk of bias was low for the flow and timing domain. The evidence was downgraded by one point.

[b] There was low concern about applicability. Given the tests' high specificity and ability to provide results within a matter of days, the tests might improve patients' outcomes by enabling earlier initiation of appropriate therapy. The evidence was not downgraded.

[c] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies.

[d] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction.

Table 43. Accuracy of LPAs for detecting rifampicin resistance by indirect testing of *Mycobacterium tuberculosis* complex culture isolates compared with a composite reference standard

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan).The tests were performed by indirect testing of *Mycobacterium tuberculosis* complex culture isolates.

Reference standard: Composite reference standard
Studies: Case–control or cohort studies comparing LPAs with a reference standard

Sensitivity	0.95 (95% CI: 0.93–0.97)
Specificity	0.99 (95% CI: 0.99–1.00)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)		Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	
True positives (patients with rifampicin resistance)	23 studies (2 091 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious[e]	None	48 (47–48)	143 (140–145)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having rifampicin resistance)								2 (2–3)	7 (5–10)	
True negatives (patients without rifampicin resistance)	23 studies (3 392 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious[f]	None	945 (937–948)	846 (838–848)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having rifampicin resistance)								5 (2–13)	4 (2–12)	

[a] The QUADAS-2 tool was used to assess the risk of bias. In total, 8/23 studies were cross-sectional; 8/23 were case–control; and 7 studies had an unclear design.

[b] The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (12/23 studies), because the method of patient sampling was unspecified (for example, consecutive or random). Additionally, 8/23 studies were assessed as having a high risk of bias due to the use of a case–control design. Also, there was uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (14/23 and 15/23, respectively). The risk of bias was low for the flow and timing domain. The evidence was downgraded by one point.

[c] Applicability was judged to be of low concern in the majority of studies because the population and the use of the index test matched the population of interest and the settings of intended use. The evidence was not downgraded.

[d] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies. The evidence was not downgraded.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction. The evidence was not downgraded.

[f] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction. The evidence was not downgraded.

Table 44. Accuracy of LPAs by direct testing for detecting isoniazid resistance in patients with signs and symptoms of TB

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan). The tests were performed by direct testing on smear-positive specimens.

Reference standard: Culture-based drug-susceptibility testing
Studies: Case–control or cohort studies comparing LPAs with a reference standard

Sensitivity	0.89 (95% CI: 0.86–0.92)
Specificity	0.98 (95% CI: 0.97–0.99)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%	
True positives (patients with isoniazid resistance)	46 studies (3 576 patients)	Cohort and case–control- type studies	Serious [a]	Not serious [b]	Not serious [c]	Not serious [d]	None	45 (43–46)	134 (129–138)	803 (772–827)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having isoniazid resistance)								5 (4–7)	16 (12–21)	97 (73–128)	
True negatives (patients without isoniazid resistance)	46 studies (6 896 patients)	Cross-sectional (cohort-type accuracy study)	Serious [a]	Not serious [b]	Not serious [c]	Not serious [e]	None	935 (926–940)	836 (829–841)	98 (97–99)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								15 (10–24)	14 (9–21)	2 (1–3)	

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%	
classified as having isoniazid resistance)											

[a] The QUADAS-2 tool was used to assess the risk of bias. The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (32/47 studies), because the method of patient sampling was unspecified (for example, consecutive or random). There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (30/47 and 32/47, respectively). The risk of bias was low for the flow and timing domain.

[b] Applicability was judged to be of low concern in the majority of studies because the population and the use of the index test matched the population of interest and the settings of intended use.

[c] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies.

[d] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction and the number of resistant specimens tested was < 15.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction and the number of sensitive specimens tested was < 15.

Table 45. Accuracy of LPAs for detecting isoniazid resistance by indirect testing of *Mycobacterium tuberculosis* complex culture isolates

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan). The tests were performed by indirect testing on *Mycobacterium tuberculosi*s complex culture isolates.

Reference standard: Culture-based drug-susceptibility testing
Studies: Case–control or cohort studies comparing LPAs with a reference standard

Sensitivity	0.91 (95% CI: 0.89–0.93)
Specificity	1.00 (95% CI: 0.99–1.00)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistenc y	Imprecision	Publicati on bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%	
True positives (patients with isoniazid resistance)	43 studies (4 559 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious[e]	None	46 (44–47)	137 (133–140)	819 (797–837)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having isoniazid resistance)								4 (3–6)	13 (10–17)	81 (63–103)	
True negatives (patients without isoniazid resistance)	43 studies (5 903 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious[f]	None	947 (943–950)	847 (844–850)	100 (99–100)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								3 (0–7)	3 (0–6)	0 (0–1)	

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistenc y	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%	
classified as having isoniazid resistance)											

[a] The QUADAS-2 tool was used to assess the risk of bias. In total, 21/43 datasets were cross-sectional; 8/43 were case–control; 2/43 datasets evaluated only strains from cases known to have MDR-TB without testing any controls; and 12/43 studies had an unclear design (for example, this includes studies in which the method of participant selection was unclear or there was uncertainty about whether specimens had been chosen for their resistance pattern).

[b] The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (21/43 studies), because the method of patient sampling was unspecified (for example, consecutive or random). There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (33/43 and 33/43, respectively). The risk of bias was low for the flow and timing domain.

[c] Applicability was judged to be of low concern in the majority of studies because the population and the use of the index test matched the population of interest and the settings of intended use.

[d] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction and the number of resistant specimens tested was < 15.

[f] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction and the number of sensitive specimens tested was < 15.

Table 46. Accuracy of LPAs for detecting isoniazid resistance in patients with signs and symptoms of TB compared with a composite reference standard

Participants: Patients with signs and symptoms of TB
Prior testing: None
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan)

Reference standard: Composite reference standard
Studies: Case–control or cohort studies comparing LPAs with a composite reference standard

Sensitivity	0.85 (95% CI: 0.81–0.89)
Specificity	1.00 (95% CI: 1.00–1.00)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%f	
True positives (patients with isoniazid resistance)	24 studies (2 346 patients)	Cohort and case–control-type studies	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None	43 (40–44)	128 (121–133)	766 (727–797)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having isoniazid resistance)								7 (6–10)	22 (17–29)	134 (103–173)	
True negatives (patients without isoniazid resistance)	24 studies (2 170 patients)	Cohort and case–control-type studies	Serious[a]	Not serious[b]	Not serious	Not serious[e]	None	949 (946–950)	849 (847–850)	100 (100–100)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								1 (0–4)	1 (0–3)	0 (0–0)	

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			Test accuracy quality of evidence
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 15%	Pre-test probability of 90%[f]	
classified as having isoniazid resistance)											

[a] The QUADAS-2 tool was used to assess the risk of bias. The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (13/24 studies), because the method of patient sampling was unspecified (for example, consecutive or random). Also, 9/24 studies were assessed as having a high risk of bias. There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (63/90 and 65/90, respectively). The risk of bias was low for the flow and timing domain. The evidence was downgraded by one point.

[b] Applicability was judged to be of low concern in the majority of studies because the population and the use of the index test matched the population of interest and the settings of intended use. The evidence was not downgraded.

[c] Although some heterogeneity was noted, this was predominantly driven by a few, small outlier studies. The evidence was not downgraded.

[d] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction. The evidence was not downgraded.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 5% in either direction. The evidence was not downgraded.

[f] A 90% prevalence was chosen to reflect the scenario in which molecular drug-susceptibility testing has already identified rifampicin resistance – that is, when the negative predictive value of this test is lower.

Table 47. Accuracy of LPAs for diagnosing MDR-TB on all specimen types by direct and indirect testing

Participants: Patients with signs and symptoms of TB
Prior testing: No
Role: Replacement test for culture-based drug-susceptibility testing
Settings: Intermediate- or central-level laboratories
Index (new) tests: GenoType MTBDR*plus* version 1 assay (Hain Lifesciences, Nehren, Germany); GenoType MTBDR*plus* version 2 assay (Hain Lifesciences, Nehren, Germany); Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan). The tests were performed on all types of specimens using direct and indirect testing.

Reference standard: Culture-based drug-susceptibility testing
Studies: Case–control or cohort studies comparing LPAs with a reference standard

Sensitivity	0.93 (95% CI: 0.90–0.95)
Specificity	0.99 (95% CI: 0.99–1.00)

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			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 MDR-TB)	60 studies (4 248 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious[e]	None	9 (9–9)	46 (45–47)	93 (90–95)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having MDR-TB)								1 (1–1)	4 (3–5)	7 (5–10)	
True negatives (patients without MDR-TB)	60 studies (8 785 patients)	Cohort and case–control-type studies[a]	Serious[b]	Not serious[c]	Not serious[d]	Not serious	None	983 (977–986)	943 (938–946)	894 (888–896)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								7 (4–13)	7 (4–12)	6 (4–12)	

Outcome	Number of studies (number of patients)	Study design	Factors that may decrease the quality of evidence					Effect per 1 000 patients tested (number of patients)			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%	
classified as having MDR-TB)											

[a] In total, 37/60 studies were cross-sectional; 8/60 studies used a case–control or cases-only design; and 15/60 studies had an unclear design.

[b] The QUADAS-2 tool was used to assess methodological quality. The risk of bias was unclear for many studies, primarily with respect to the patient-selection domain (34/60 studies), because the method of patient sampling was unspecified (for example, consecutive or random); the risk of bias was considered to be high for the 12 studies that used a case–control design. There was also uncertainty in the index-test and reference-test domains because many studies did not specify whether the operators of the index test and the reference test were blinded to the results of the other test (37/60 and 39/60, respectively). The risk of bias was low for the flow and timing domain. The evidence was downgraded by one point.

[c] Applicability was judged to be of low concern in the majority of studies because the population and the use of the index test matched the population of interest and the settings of intended use.

[d] Although some heterogeneity was noted for sensitivity, this was predominantly driven by a few, small outlier studies. The estimates for specificity were more homogeneous. The evidence was not downgraded.

[e] Imprecision was considered to be present when the pooled confidence intervals were wider than 10% in either direction. The evidence was not downgraded.

2.7 GRADE profiles: Second-line line probe assay (SL-LPA)

Table 48. Accuracy of MTBDR*sl* by direct testing for detection of fluoroquinolone (FQ) resistance in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*sl* by direct testing for detection of FQ resistance in patients with rifampicin-resistant or MDR-TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*sl* testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*sl* (version 1.0).[5] The test was performed by direct testing on smear-positive specimens
Reference standard: Culture-based drug susceptibility testing
Studies: Mainly cross-sectional studies

Sensitivity	0.86 (95% CI: 0.75 to 0.93)
Specificity	0.99 (95% CI: 0.97 to 0.99)

Prevalences	5%	10%	15%

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with FQ resistance)	9 studies 519 patients	cross-sectional (cohort type accuracy study) [1]	not serious [2]	not serious [3]	serious [4]	not serious	none	43 (37 to 47)	86 (75 to 93)	129 (112 to 140)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having FQ resistance)								7 (3 to 13)	14 (7 to 25)	21 (10 to 38)	
True negatives (patients without FQ resistance)	9 studies 1252 patients	cross-sectional (cohort type accuracy study) [1]	not serious [2]	not serious [3]	not serious	not serious	none	937 (921 to 944)	887 (872 to 895)	838 (824 to 845)	⊕⊕⊕⊕ HIGH

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
False positives (patients incorrectly classified as having FQ resistance)								13 (6 to 29)	13 (5 to 28)	12 (5 to 26)	

Footnotes

1. Eight studies used a cross-sectional study design and one study used a case-control study design.
2. The QUADAS-2 tool was used to assess the risk of bias. All studies used consecutive sampling. In seven studies, the reader of the index test was blinded to results of the reference standard and in two studies information about blinding to the reference standard was not reported. Several studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. This may have lowered specificity, but this was not observed. The evidence was not downgraded.
3. There was low concern for applicability. Given that the test's high specificity and ability to provide results within a matter of days, the test might improve patient outcomes by enabling earlier initiation of appropriate therapy. The evidence was not downgraded.
4. For individual studies, sensitivity estimates ranged from 33% to 100%. One small study with the lowest sensitivity only included three fluoroquinolone-resistant patients. However, the remaining heterogeneity could not be explained by study quality or other factors. The evidence was downgraded one point
5. This systematic review mainly evaluated MTBDR*sl* (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*sl* (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*sl* (version 1.0). Therefore the findings in this review should be considered applicable to the test.

Table 49. Accuracy of MTBDR*s*/ by direct testing for detection of second-line injectable drugs (SLID) resistance in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*s*/ by direct testing for detection of SLID resistance in patients with rifampicin-resistant or MDR-TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*s*/ testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*s*/ (version 1.0).[5] The test was performed by direct testing on smear-positive specimens
Reference standard: Culture-based drug susceptibility testing
Studies: Mainly cross-sectional studies

Sensitivity	0.87 (95% CI: 0.38 to 0.99)
Specificity	0.99 (95% CI: 0.94 to 1.00)

Prevalences	5%	10%	15%

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with SLID resistance)	8 studies 348 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	not serious [3]	serious [4]	none	44 (19 to 49)	87 (38 to 99)	131 (57 to 148)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having SLID resistance)								6 (1 to 31)	13 (1 to 62)	19 (2 to 93)	
True negatives (patients without SLID resistance)	8 studies 1291 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	not serious	not serious	none	945 (889 to 950)	896 (842 to 900)	846 (796 to 850)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having SLID resistance)								5 (0 to 61)	4 (0 to 58)	4 (0 to 54)	

Footnotes

1. The QUADAS-2 was used to assess the risk of bias. All studies used consecutive or random sampling. In six studies, the reader of the index test was blinded to results of the reference standard in two studies information about blinding to the reference standard was not reported. Fifty percent of the studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. The evidence was downgraded by one point.
2. There was low concern for applicability. Given the test's high specificity and ability to provide results within a matter of days, the test might improve patient outcomes by enabling earlier initiation of appropriate therapy. The evidence was not downgraded.
3. For individual studies, sensitivity estimates ranged from 9% to 100%. The variability was explained in part by the use of different drugs, critical concentrations, and types of culture media in the reference standard and likely presence of *eis* resistance-conferring mutations in patients in Eastern European countries. The evidence was not downgraded and considered this in the context of other factors, in particular imprecision.
4. The wide confidence interval around true positives and false negatives may lead to different decisions depending on which confidence limits are assumed. The evidence was downgraded by one point.
5. This systematic review mainly evaluated MTBDR*s*l (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*s*l (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*s*l (version 1.0). Therefore the findings in this review should be considered applicable to the test.

Table 50. Accuracy of MTBDR*s*/ by indirect testing for detection of FQ resistance in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*s*/ by indirect testing for detection of FQ resistance in patients with rifampicin-resistant or MDR-TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*s*/ testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*s*/ (version 1.0).[5] The test was performed by indirect testing on culture isolates
Reference standard: Culture-based drug susceptibility testing
Studies: Cross-sectional and case-control studies

Sensitivity	0.86 (95% CI: 0.79 to 0.90)
Specificity	0.99 (95% CI: 0.97 to 0.99)

Prevalences	5%	10%	15%

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 10%	Pre-test probability of 15%	
True positives (patients with FQ resistance)	19 studies 869 patients	cohort & case-control type studies [1]	not serious [2]	serious [3]	serious [4]	not serious	none	43 (40 to 45)	86 (79 to 90)	128 (119 to 136)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having FQ resistance)								7 (5 to 10)	14 (10 to 21)	22 (14 to 31)	
True negatives (patients without FQ resistance)	19 studies 1354 patients	cohort & case-control type studies [1]	not serious [2]	serious [3]	not serious	not serious	none	937 (921 to 944)	887 (872 to 895)	838 (824 to 845)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having FQ resistance)								13 (6 to 29)	13 (5 to 28)	12 (5 to 26)	

Footnotes

1. Thirteen studies used a cross-sectional study design and six studies used a case-control design. A sensitivity analysis that only included cross-sectional studies found sensitivity and specificity estimates similar to those for all studies.
2. The QUADAS-2 tool was used to assess the risk of bias. Fourteen studies used consecutive or random sampling. In 12 studies, the reader of the test was blinded to results of the reference standard. The majority of studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. The evidence was downgraded by one point.
3. Several studies included patients (such as known drug-susceptible patients) that did not match the review question. Indirectness was considered in the context of other factors, including the different critical concentrations used for culture-based drug susceptibility testing. The evidence was downgraded by one point.
4. For individual studies, sensitivity estimates ranged from 57% to 100%. Some of the variability in sensitivity might be explained by the use of different drugs, different critical concentrations, and different types of culture media in the reference standard. However, some of the variability remained unexplained. The evidence was downgraded by one point.
5. This systematic review mainly evaluated MTBDR*s*l (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*s*l (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*s*l (version 1.0). Therefore the findings in this review should be considered applicable to the test.

Table 51. Accuracy of MTBDR*sl* by indirect testing for detection of SLID resistance in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*sl* by indirect testing for detection of SLID resistance in patients with rifampicin-resistant or MDR-TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*sl* testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*sl* (version 1.0).[5] The test was performed by indirect testing on culture isolates
Reference standard: Culture-based drug susceptibility testing
Studies: Cross-sectional and case-control studies

Sensitivity	0.77 (95% CI: 0.63 to 0.86)
Specificity	0.99 (95% CI: 0.97 to 1.00)

Prevalences	5%	10%	15%

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 10%	pre-test probability of 15%	
True positives (patients with SLID resistance)	16 studies 575 patients	cohort & case-control type studies [1]	serious [2]	serious [3]	serious [4]	not serious	none	38 (32 to 43)	77 (63 to 86)	115 (95 to 129)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having SLID resistance)								12 (7 to 18)	23 (14 to 37)	35 (21 to 55)	
True negatives (patients without SLID resistance)	16 studies 1346 patients	cohort & case-control type studies [1]	serious [2]	serious [3]	not serious	not serious	none	941 (924 to 947)	892 (876 to 897)	842 (827 to 847)	⊕⊕◯◯ LOW

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 5%	pre-test probability of 10%	pre-test probability of 15%	
False positives (patients incorrectly classified as having SLID resistance)								9 (3 to 26)	8 (3 to 24)	8 (3 to 23)	

Footnotes

1. Ten studies were cross-sectional design and six studies were case-control design. A sensitivity analysis that only included cross-sectional studies found sensitivity and specificity estimates similar to those for all studies.
2. The QUADAS-2 tool was used to assess the risk of bias. Eleven studies used consecutive or random sampling. In ten studies, the reader of the test was blinded to results of the reference standard. The majority of studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. The evidence was downgraded by one point.
3. Several studies included patients (drug-susceptible) that did not match the review question. Indirectness was considered in the context of other factors, including the different critical concentrations used for culture-based drug susceptibility testing. The evidence was downgraded by one point.
4. For individual studies, sensitivity estimates ranged from 25% to 100%. Some of the variability could be explained by the use of different drugs, critical concentrations, and types of culture media in the reference standard and by presence of the *eis* mutation in patients from Eastern Europe. *eis* gene is not targeted by version 1.0 of the test, which may lead to lower sensitivity among Eastern European strains. However, some of the variability remained unexplained. The evidence was downgraded by one point.
5. This systematic review mainly evaluated MTBDR*sl* (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*sl* (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*sl* (version 1.0). Therefore the findings in this review should be considered applicable to the test.

Table 52. Accuracy of MTBDR*sl* by direct testing for the diagnosis of XDR-TB in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*sl* by direct testing for the diagnosis of XDR-TB in patients with rifampicin-resistant or MDR-TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*sl* testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*sl* (version 1.0).[5] The test was performed by indirect testing on culture isolates
Reference standard: Culture-based drug susceptibility testing
Studies: Cross-sectional and case-control studies

Sensitivity	0.69 (95% CI: 0.39 to 0.89)
Specificity	0.99 (95% CI: 0.95 to 0.99)

Prevalences	1%	5%	10%

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			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 XDR-TB)	6 studies 143 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	not serious [3]	serious [4]	none	7 (4 to 9)	35 (19 to 45)	69 (39 to 89)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having XDR-TB)								3 (1 to 6)	15 (5 to 31)	31 (11 to 61)	
True negatives (patients without XDR-TB)	6 studies 1277 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [2]	not serious	not serious	none	980 (941 to 983)	941 (903 to 943)	891 (855 to 894)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								10 (7 to 49)	9 (7 to 47)	9 (6 to 45)	

Outcome	Number of studies (Number of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 1%	Pre-test probability of 5%	Pre-test probability of 10%	
classified as having XDR-TB)											

Footnotes

1. The QUADAS-2 tool was used to assess the risk of bias. All studies used consecutive sampling. In four studies, the reader of the test was blinded to results of the reference standard and in two studies information about blinding was not reported. The majority of studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. The evidence was downgraded by one point.
2. There was low concern for applicability. Given the test's high specificity and ability to provide results within a matter of days, the test might improve patient outcomes by enabling earlier initiation of appropriate therapy. The evidence was not downgraded.
3. For individual studies, sensitivity estimates ranged from 14% to 92%. We thought variability could be explained in part by the use of different drugs, critical concentrations, and types of culture media in the reference standard and likely presence of *eis* mutation in patients in Eastern European countries. The evidence was not downgrade and considered this in the context of other factors, in particular imprecision.
4. The very wide 95% CI for true positives and false negatives may lead to different decisions depending on which confidence limits are assumed. The evidence was downgraded by one point.
5. This systematic review mainly evaluated MTBDR*sl* (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*sl* (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*sl* (version 1.0). Therefore the findings in this review should be considered applicable to the test.

Table 53. Accuracy of MTBDR*s*/ by indirect testing for the diagnosis of XDR-TB in patients with rifampicin-resistant or MDR-TB

Question: What is the diagnostic accuracy of MTBDR*s*/ by indirect testing for the diagnosis of XDR-TB in patients with rifampicin-resistant or MDR- TB?
Participants: patients with rifampicin-resistant or MDR-TB
Prior testing: Patients who received MTBDR*s*/ testing will first have received smear microscopy, Xpert MTB/RIF or other nucleic acid amplification test, and culture to diagnose TB detection and Xpert MTB/RIF, MTBDR*plus* (version 2.0) or an alternative line-probe assay to detect first-line drug resistance
Role: Replacement test for culture-based drug susceptibility testing
Settings: Intermediate or central level laboratories
Index (new) test: MTBDR*s*/ (version 1.0).[6] The test was performed by indirect testing on culture isolates
Reference standard: Culture-based drug susceptibility testing
Studies: Cross-sectional and case-control studies

Sensitivity	0.69 (95% CI: 0.39 to 0.89)
Specificity	0.99 (95% CI: 0.95 to 0.99)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			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 XDR-TB)	8 studies 173 patients	cohort & case-control type studies [1]	serious [2]	serious [3]	serious [4]	not serious [5]	none	7 (4 to 9)	35 (19 to 45)	69 (39 to 89)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having XDR-TB)								3 (1 to 6)	15 (5 to 31)	31 (11 to 61)	
True negatives (patients without XDR-TB)	8 studies 707 patients	cohort & case-control type studies [1]	serious [2]	serious [3]	not serious [4]	not serious	none	980 (941 to 983)	941 (903 to 943)	891 (855 to 894)	⊕⊕◯◯ LOW
False positives (patients incorrectly								10 (7 to 49)	9 (7 to 47)	9 (6 to 45)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested			Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 5%	pre-test probability of 10%	
classified as having XDR-TB)											

Footnotes

1. Four studies were cross-sectional design and four were case-control design.
2. The QUADAS-2 tool was used to assess the risk of bias. Six studies used consecutive sampling. In six studies, the reader of the test was blinded to results of the reference standard. All studies used critical concentrations for the phenotypic culture-based reference standard that differed from the concentrations recommended by WHO. The evidence was downgraded one point.
3. Several studies included patients (drug-susceptible) that did not match the review question. Indirectness was considered in the context of other factors, including the different critical concentrations used for culture-based drug susceptibility testing. The evidence was downgraded one point.
4. For individual studies, sensitivity estimates ranged from 20% to 100%. Some of the variability could be explained by the use of different drugs, critical concentrations, and types of culture media in the reference standard and by presence of the *eis* mutation in patients in Eastern Europe. eis gene is not targeted by version 1.0 of the test, which may lead to lower sensitivity in Eastern European strains. However, some of the variability remained unexplained. The evidence was downgraded one point.
5. The wide confidence interval around true positives and false negatives may lead to different decisions depending on which confidence limits are assumed. The evidence was not further downgraded as one point was deducted for inconsistency.
6. This systematic review mainly evaluated MTBDR*sl* (version 1.0), which has recently been replaced with version 2.0. The addition of new probes targeting more known resistance-conferring mutations in the MTBDR*sl* (version 2.0) would be expected to yield a diagnostic accuracy at least the same as or higher than that of MTBDR*sl* (version 1.0). Therefore the findings in this review should be considered applicable to the test.

2.8 GRADE profiles: High complexity reverse hybridization-based NAATs

Table 54: Should High complexity hybridization based NAATs on isolates be used to diagnose PZA resistance in patients with microbiologically confirmed PTB, irrespective of resistance to RIF, pDST?

Sensitivity	0.81 (95% CI: 0.75 to 0.86)
Specificity	0.98 (95% CI: 0.96 to 0.99)

Prevalences	8%	50%	90%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 50%	pre-test probability of 90%	
True positives (patients with PZA resistance)	7 studies 214 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	serious [c]	not serious	none	65 (60 to 69)	406 (377 to 429)	731 (679 to 772)	⨁◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having PZA resistance)								15 (11 to 20)	94 (71 to 123)	169 (128 to 221)	
True negatives (patients without PZA resistance)	7 studies 750 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	not serious	none	900 (888 to 907)	489 (483 to 493)	98 (96 to 99)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having PZA resistance)								20 (13 to 32)	11 (7 to 17)	2 (1 to 4)	

Explanations

a. Studies suffered from selection bias, as they selected isolates with a wide range of different pncA mutations instead of a representative sample from a population. We downgraded one level for risk of bias.

b. Studies included do not directly address the review question. We downgraded one level for indirectness.
c. Burhan trial and Rienthong study are outliers for their sensitivities compared to the other studies. We downgraded one level for inconsistency.

2.9 GRADE profiles: Targeted NGS

Table 55: Should TNGS as an initial test be used to diagnose drug resistance to rifampin (RIF) (composite) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.93 (95% CI: 0.87 to 0.99)
Specificity	0.96 (95% CI: 0.89 to 1.00)

Prevalences	2%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2%	pre-test probability of10%	pre-test probability of15%	
True positives (patients with drug resistance to rifampin (RIF) (composite))	9 studies 1436 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	19 (17 to 20)	93 (87 to 99)	140 (131 to 149)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to rifampin (RIF) (composite))								1 (0 to 3)	7 (1 to 13)	10 (1 to 19)	
True negatives (patients without drug resistance to rifampin (RIF) (composite))	7 studies 271 patients[b]	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	serious[c]	none	941 (872 to 980)	864 (801 to 900)	816 (757 to 850)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having drug resistance to rifampin (RIF) (composite))								39 (0 to 108)	36 (0 to 99)	34 (0 to 93)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to rifampicin (composite) across data used in the model was 83% (CI 81% to 85%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.
b. 115 observations from ONT dropped by model as variable 'duplicate=2' (i.e. ONT) predicts the outcome perfectly (115 TN results)
c. 95% confidence interval for specificity spans >10%

Table 56: Should TNGS as the initial test be used to diagnose drug resistance to isoniazid (INH) (pDST) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.96 (95% CI: 0.93 to 0.99)
Specificity	0.97 (95% CI: 0.95 to 0.99)

Prevalences	2%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2%	pre-test probability of10%	pre-test probability of15%	
True positives (patients with drug resistance to isoniazid (INH) (pDST))	12 studies 1440 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	19 (19 to 20)	96 (93 to 99)	144 (140 to 149)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to isoniazid (INH) (pDST))								1 (0 to 1)	4 (1 to 7)	6 (1 to 10)	
True negatives (patients without drug resistance to isoniazid (INH) (pDST))	12 studies 517 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	951 (931 to 970)	873 (855 to 891)	825 (808 to 842)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having drug resistance to isoniazid (INH) (pDST))								29 (10 to 49)	27 (9 to 45)	25 (8 to 42)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to isoniazid across data used in the model was 74% (CI 72% to 76%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.

Table 57: Should TNGS as the initial test be used to diagnose drug resistance to levofloxacin (LFX) (pDST) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.94 (95% CI: 0.88 to 1.00)
Specificity	0.96 (95% CI: 0.93 to 0.99)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of5%	pre-test probability of10%	
True positives (patients with drug resistance to levofloxacin (LFX) (pDST))	6 studies 654 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	serious[b]	not serious	none	9 (9 to 10)	47 (44 to 50)	94 (88 to 100)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to levofloxacin (LFX) (pDST))								1 (0 to 1)	3 (0 to 6)	6 (0 to 12)	
True negatives (patients without drug resistance to levofloxacin (LFX) (pDST))	7 studies 913 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	950 (921 to 980)	912 (884 to 941)	864 (837 to 891)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having drug resistance to levofloxacin (LFX) (pDST))								40 (10 to 69)	38 (9 to 66)	36 (9 to 63)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to Levofloxacin across data used in the model was 42% (CI 39% to 44%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.

b. One of the larger studies performed much worse for sensitivity

Table 58: Should TNGS as the initial test be used to diagnose drug resistance to moxifloxacin (MFX) (pDST) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.96 (95% CI: 0.92 to 0.99)
Specificity	0.96 (95% CI: 0.93 to 1.00)

Prevalences	1%	5%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of5%	pre-test probability of10%	
True positives (patients with drug resistance to moxifloxacin (MFX) (pDST))	6 studies 652 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	10 (9 to 10)	48 (46 to 50)	96 (92 to 99)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to moxifloxacin (MFX) (pDST))								0 (0 to 1)	2 (0 to 4)	4 (1 to 8)	
True negatives (patients without drug resistance to moxifloxacin (MFX) (pDST))	8 studies 921 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	950 (921 to 990)	912 (884 to 950)	864 (837 to 900)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having drug resistance to moxifloxacin (MFX) (pDST))								40 (0 to 69)	38 (0 to 66)	36 (0 to 63)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to Moxifloxacin across data used in the model was 41% (CI 39% to 44%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.

Table 59: Should TNGS as the initial test be used to diagnose drug resistance to pyrazinamide (PZA) (composite) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.88 (95% CI: 0.85 to 0.92)
Specificity	0.99 (95% CI: 0.97 to 1.00)

Prevalences	1%	3%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of3%	pre-test probability of10%	
True positives (patients with drug resistance to pyrazinamide (PZA) (composite))	3 studies 346 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	9 (9 to 9)	26 (26 to 28)	88 (85 to 92)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to pyrazinamide (PZA) (composite))								1 (1 to 1)	4 (2 to 4)	12 (8 to 15)	
True negatives (patients without drug resistance to pyrazinamide (PZA) (composite))	3 studies 269 patients	cross-sectional (cohort type accuracy study)	not serious[a]	serious[a]	not serious	not serious	none	980 (960 to 990)	960 (941 to 970)	891 (873 to 900)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having drug resistance to pyrazinamide (PZA) (composite))								10 (0 to 30)	10 (0 to 29)	9 (0 to 27)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to Pyrazinamide (composite) across data used in the model was 56% (CI 52% to 60%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.

Table 60: Should TNGS as the initial test be used to diagnose drug resistance to ethambutol (EMB) (composite) in patients with bacteriologically confirmed pulmonary TB disease?

Sensitivity	0.96 (95% CI: 0.94 to 0.98)
Specificity	0.99 (95% CI: 0.98 to 1.00)

Prevalences	1%	3%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of3%	pre-test probability of10%	
True positives (patients with drug resistance to ethambutol (EMB) (composite))	4 studies 432 patients	cross-sectional (cohort type accuracy study)	serious[a,b]	serious[a]	not serious	not serious	none	10 (9 to 10)	29 (28 to 29)	96 (94 to 98)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to ethambutol (EMB) (composite))								0 (0 to 1)	1 (1 to 2)	4 (2 to 6)	
True negatives (patients without drug resistance to ethambutol (EMB) (composite))	4 studies 268 patients[c]	cross-sectional (cohort type accuracy study)	serious[a,b]	serious[a]	not serious	not serious	none	980 (970 to 990)	960 (951 to 970)	891 (882 to 900)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having drug resistance to ethambutol (EMB) (composite))								10 (0 to 20)	10 (0 to 19)	9 (0 to 18)	

Explanations

a. All studies enriched for samples that were rifampicin resistant. Prevalence of resistance to ethambutol (composite) across data used in the model was 62% (CI 58% to 65%). However, prevalence should not significantly impact sensitivity or specificity, therefore not downgraded for bias, just for indirectness.

b. Different samples used for tNGS and reference test

c. The model does not control for rifampicin resistance as this variable was collinear in the original model.

Table 61: Should TNGS be used to diagnose drug resistance to isoniazid (INH) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.96 (95% CI: 0.94 to 0.99)
Specificity	0.96 (95% CI: 0.92 to 1.00)

Prevalences	60%	75%	90%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of60%	pre-test probability of75%	pre-test probability of90%	
True positives (patients with drug resistance to isoniazid (INH) (pDST))	12 studies 1440 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	576 (564 to 594)	720 (705 to 742)	864 (846 to 891)	⨁⨁⨁⨁ High
False negatives (patients incorrectly classified as not having drug resistance to isoniazid (INH) (pDST))								24 (6 to 36)	30 (8 to 45)	36 (9 to 54)	
True negatives (patients without drug resistance to isoniazid (INH) (pDST))	12 studies 517 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	384 (368 to 400)	240 (230 to 250)	96 (92 to 100)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to isoniazid (INH) (pDST))								16 (0 to 32)	10 (0 to 20)	4 (0 to 8)	

Explanations

a. Prevalence of resistance to isoniazid across data used in the model was 74% (CI 72% to 76%)

Table 62: Should TNGS be used to diagnose drug resistance to levofloxacin (LFX) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.96 (95% CI: 0.90 to 1.00)
Specificity	0.96 (95% CI: 0.93 to 0.99)

Prevalences	10%	30%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10%	pre-test probability of30%	pre-test probability of50%	
True positives (patients with drug resistance to levofloxacin (LFX) (pDST))	6 studies 654 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	serious[b]	not serious	none	96 (90 to 100)	288 (270 to 300)	480 (450 to 500)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to levofloxacin (LFX) (pDST))								4 (0 to 10)	12 (0 to 30)	20 (0 to 50)	
True negatives (patients without drug resistance to levofloxacin (LFX) (pDST))	7 studies 913 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	864 (837 to 891)	672 (651 to 693)	480 (465 to 495)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to levofloxacin (LFX) (pDST))								36 (9 to 63)	28 (7 to 49)	20 (5 to 35)	

Explanations

a. Prevalence of resistance to levofloxacin across data used in the model was 42% (CI 39% to 44%)
b. One outlying study for sensitivity

Table 63: Should TNGS be used to diagnose drug resistance to moxifloxacin (MFX) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.97 (95% CI: 0.94 to 1.00)
Specificity	0.95 (95% CI: 0.91 to 0.99)

Prevalences	10%	30%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10%	pre-test probability of30%	pre-test probability of50%	
True positives (patients with drug resistance to moxifloxacin (MFX) (pDST))	6 studies 652 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	97 (94 to 100)	291 (282 to 300)	485 (470 to 500)	⨁⨁⨁⨁ High
False negatives (patients incorrectly classified as not having drug resistance to moxifloxacin (MFX) (pDST))								3 (0 to 6)	9 (0 to 18)	15 (0 to 30)	
True negatives (patients without drug resistance to moxifloxacin (MFX) (pDST))	8 studies 921 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	855 (819 to 891)	665 (637 to 693)	475 (455 to 495)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to moxifloxacin (MFX) (pDST))								45 (9 to 81)	35 (7 to 63)	25 (5 to 45)	

Explanations

a. Prevalence of resistance to moxifloxcin across data used in the model was 41% (CI 39% to 44%)

Table 64: Should TNGS be used to diagnose drug resistance to pyrazinamide (PZA) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.90 (95% CI: 0.85 to 0.95)
Specificity	0.90 (95% CI: 0.86 to 0.94)

Prevalences	30%	50%	90%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of30%	pre-test probability of50%	pre-test probability of90%	
True positives (patients with drug resistance to pyrazinamide (PZA) (pDST))	6 studies 425 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious[a]	not serious	none	270 (255 to 285)	450 (425 to 475)	810 (765 to 855)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having drug resistance to pyrazinamide (PZA) (pDST))								30 (15 to 45)	50 (25 to 75)	90 (45 to 135)	
True negatives (patients without drug resistance to pyrazinamide (PZA) (pDST))	6 studies 379 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	630 (602 to 658)	450 (430 to 470)	90 (86 to 94)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to pyrazinamide (PZA) (pDST))								70 (42 to 98)	50 (30 to 70)	10 (6 to 14)	

Explanations

a. One study is an outlier for sensitivity

Table 65: Should TNGS be used to diagnose drug resistance to bedaquiline (BDQ) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.68 (95% CI: 0.43 to 0.93)
Specificity	0.97 (95% CI: 0.94 to 1.00)

Prevalences	1%	3%	5%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of3%	pre-test probability of5%	
True positives (patients with drug resistance to bedaquiline (BDQ) (pDST))	3 studies 31 patients[a]	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	not serious[c]	very serious[d]	none	7 (4 to 9)	20 (13 to 28)	34 (22 to 47)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to bedaquiline (BDQ) (pDST))								3 (1 to 6)	10 (2 to 17)	16 (3 to 28)	
True negatives (patients without drug resistance to bedaquiline (BDQ) (pDST))	4 studies 519 patients[e]	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	not serious	not serious	none	960 (931 to 990)	941 (912 to 970)	922 (893 to 950)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to bedaquiline (BDQ) (pDST))								30 (0 to 59)	29 (0 to 58)	28 (0 to 57)	

c. Explanations

a. This model is not controlled for CT value as that variable was collinear in the original model
b. Prevalence of resistance to bedaquiline across data used in the model was 6% (CI 4% to 8%)
c. One study had very low sensitivity but it only had 3 resistant samples. It identified 0/3.
d. Very wide 95% confidence intervals for sensitivity
e. This model is not controlled for rifampicin resistance as this variable was collinear in the original model. Instead, the data have been restricted to isolated that are resistant to rifampicin by Xpert, and then controlled for CT value.

Table 66: Should TNGS be used to diagnose drug resistance to linezolid (LZD) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.69 (95% CI: 0.39 to 0.99)
Specificity	1.00 (95% CI: 1.00 to 1.00)

Prevalences	1%	3%	5%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of3%	pre-test probability of5%	
True positives (patients with drug resistance to linezolid (LZD) (pDST))	4 studies 31 patients[a]	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	not serious[c]	very serious[d]	none	7 (4 to 10)	21 (12 to 30)	34 (20 to 50)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to linezolid (LZD) (pDST))								3 (0 to 6)	9 (0 to 18)	16 (0 to 30)	
True negatives (patients without drug resistance to linezolid (LZD) (pDST))	6 studies 1093 patients[e]	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	not serious	not serious	none	990 (990 to 990)	970 (970 to 970)	950 (950 to 950)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to linezolid (LZD) (pDST))								0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Explanations

a. This model is restricted to isolates that were resistant to rifampicin by Xpert, and controls for CT value
b. Prevalence of resistance to linezolid across data used in the model was 3% (CI 2% to 4%)
c. One study was an outlier for sensitivity but only had 1 resistant sample (0/1 detected).
d. Very wide 95% confidence intervals
e. This model is restricted to isolates that were resistant to rifampicin by Xpert, and does not control for CT value as both variables were collinear in the original model

Table 67: Should TNGS be used to diagnose drug resistance to clofazimine (CFZ) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.70 (95% CI: 0.35 to 1.00)
Specificity	0.96 (95% CI: 0.93 to 0.99)

Prevalences	1%	3%	5%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of1%	pre-test probability of3%	pre-test probability of5%	
True positives (patients with drug resistance to clofazimine (CFZ) (pDST))	4 studies 36 patients[a]	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	serious[c]	serious[d]	none	7 (3 to 10)	21 (10 to 30)	35 (17 to 50)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to clofazimine (CFZ) (pDST))								3 (0 to 7)	9 (0 to 20)	15 (0 to 33)	
True negatives (patients without drug resistance to clofazimine (CFZ) (pDST))	6 studies 789 patients	cross-sectional (cohort type accuracy study)	not serious[b]	not serious	not serious	not serious	none	950 (921 to 980)	931 (902 to 960)	912 (884 to 941)	⨁⨁⨁⨁ High
False positives (patients incorrectly classified as having drug resistance to clofazimine (CFZ) (pDST))								40 (10 to 69)	39 (10 to 68)	38 (9 to 66)	

Explanations

a. Model not controlled for CT value as this was collinear in the original model
b. Prevalence of resistance to clofazimine across data used in the model was 3% (CI 2% to 4%)
c. The two smaller studies are outliers for sensitivity. Downgraded as it's more than one small study.
d. Very wide 95% confidence intervals for sensitivity

Table 68: Should TNGS be used to diagnose drug resistance to amikacin (AMK) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.87 (95% CI: 0.75 to 1.00)
Specificity	0.99 (95% CI: 0.98 to 1.00)

Prevalences	5%	10%	15%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of5%	pre-test probability of10%	pre-test probability of15%	
True positives (patients with drug resistance to amikacin (AMK) (pDST))	5 studies 115 patients[a]	cross-sectional (cohort type accuracy study)	serious[b,c]	not serious	serious[d]	serious[e]	none	44 (38 to 50)	87 (75 to 100)	131 (112 to 150)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having drug resistance to amikacin (AMK) (pDST))								6 (0 to 12)	13 (0 to 25)	19 (0 to 38)	
True negatives (patients without drug resistance to amikacin (AMK) (pDST))	8 studies 1003 patients[a]	cross-sectional (cohort type accuracy study)	serious[b,c]	not serious	not serious	not serious	none	941 (931 to 950)	891 (882 to 900)	842 (833 to 850)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having drug resistance to amikacin (AMK) (pDST))								9 (0 to 19)	9 (0 to 18)	8 (0 to 17)	

Explanations

a. The model is restricted to isolated that were resistant to rifampicin by Xpert, as this was collinear in the original model, but controls for CT value
b. Prevalence of resistance to amikacin across data used in the model was 10% (CI 9% to 12%)
c. Non WHO recommended CC used
d. Two outlying studies for sensitivity, albeit small studies
e. wide 95% confidence intervals for sensitivity

Table 69: Should TNGS be used to diagnose drug resistance to ethambutol (EMB) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.91 (95% CI: 0.85 to 0.97)
Specificity	0.92 (95% CI: 0.88 to 0.96)

Prevalences	10%	30%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10%	pre-test probability of30%	pre-test probability of50%	
True positives (patients with drug resistance to ethambutol (EMB) (pDST))	1 studies 89 patients[a]	cross-sectional (cohort type accuracy study)	serious[b,c]	serious[d]	not serious	not serious	none	91 (85 to 97)	273 (255 to 291)	455 (425 to 485)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having drug resistance to ethambutol (EMB) (pDST))								9 (3 to 15)	27 (9 to 45)	45 (15 to 75)	
True negatives (patients without drug resistance to ethambutol (EMB) (pDST))	1 studies 213 patients[a]	cross-sectional (cohort type accuracy study)	serious[b,c]	serious[d]	not serious	not serious	none	828 (792 to 864)	644 (616 to 672)	460 (440 to 480)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having drug resistance to ethambutol (EMB) (pDST))								72 (36 to 108)	56 (28 to 84)	40 (20 to 60)	

Explanations

a. The model is restricted to isolated that were resistant to rifampicin by Xpert, as this was collinear in the original model, but controls for CT value

b. Different samples used for tNGS and reference test

c. Prevalence of resistance to ethambutol (pDST) across data used in the model was 29% (CI 24% to 35%)

d. Only one study (from China). Downgraded by one as may not be generalisable.

Table 70: Should TNGS be used to diagnose drug resistance to streptomycin (STR) (pDST) in patients with bacteriologically confirmed rifampin-resistant pulmonary TB disease?

Sensitivity	0.98 (95% CI: 0.96 to 1.00)
Specificity	0.75 (95% CI: 0.59 to 0.91)

Prevalences	10%	30%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of10%	pre-test probability of30%	pre-test probability of50%	
True positives (patients with drug resistance to streptomycin (STR) (pDST))	5 studies 493 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	not serious	not serious	none	98 (96 to 100)	294 (288 to 300)	490 (480 to 500)	⨁⨁⨁⨁ High
False negatives (patients incorrectly classified as not having drug resistance to streptomycin (STR) (pDST))								2 (0 to 4)	6 (0 to 12)	10 (0 to 20)	
True negatives (patients without drug resistance to streptomycin (STR) (pDST))	5 studies 250 patients	cross-sectional (cohort type accuracy study)	not serious[a]	not serious	serious[b]	serious[c]	none	675 (531 to 819)	525 (413 to 637)	375 (295 to 455)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having drug resistance to streptomycin (STR) (pDST))								225 (81 to 369)	175 (63 to 287)	125 (45 to 205)	

Explanations

a. Prevalence of resistance to streptomycin across data used in the model was 66% (CI 63% to 70%)
b. One study was an outlier
c. Wide 95% confidence intervals for specificity

For further information, please contact:
Global Tuberculosis Programme
World Health Organization
20 Avenue Appia CH-1211 Geneva 27 Switzerland
Web site: https://www.who.int/teams/
global-tuberculosis-programme/overview

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