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Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin (Review)

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[Diagnostic Test Accuracy Review]

Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin

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ABSTRACT

Background

The World Health Organization (WHO) End TB Strategy stresses universal access to drug susceptibility testing (DST). DST determines whether *Mycobacterium tuberculosis* bacteria are susceptible or resistant to drugs. Xpert MTB/XDR is a rapid nucleic acid amplification test for detection of tuberculosis and drug resistance in one test suitable for use in peripheral and intermediate level laboratories. In specimens where tuberculosis is detected by Xpert MTB/XDR, Xpert MTB/XDR can also detect resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin.

Objectives

To assess the diagnostic accuracy of Xpert MTB/XDR for pulmonary tuberculosis in people with presumptive pulmonary tuberculosis (having signs and symptoms suggestive of tuberculosis, including cough, fever, weight loss, night sweats).

To assess the diagnostic accuracy of Xpert MTB/XDR for resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin in people with tuberculosis detected by Xpert MTB/XDR, irrespective of rifampicin resistance (whether or not rifampicin resistance status was known) and with known rifampicin resistance.

Search methods

We searched multiple databases to 23 September 2021. We limited searches to 2015 onwards as Xpert MTB/XDR was launched in 2020.

Selection criteria

Diagnostic accuracy studies using sputum in adults with presumptive or confirmed pulmonary tuberculosis. Reference standards were culture (pulmonary tuberculosis detection); phenotypic DST (pDST), genotypic DST (gDST),composite (pDST and gDST) (drug resistance detection).

Data collection and analysis

Two review authors independently reviewed reports for eligibility and extracted data using a standardized form. For multicentre studies, we anticipated variability in the type and frequency of mutations associated with resistance to a given drug at the different centres and considered each centre as an independent study cohort for quality assessment and analysis. We assessed methodological quality with QUADAS-2, judging risk of bias separately for each target condition and reference standard. For pulmonary tuberculosis detection, owing to heterogeneity in participant characteristics and observed specificity estimates, we reported a range of sensitivity and specificity estimates and did not perform a meta-analysis. For drug resistance detection, we performed meta-analyses by reference standard using bivariate random-effects models. Using GRADE, we assessed certainty of evidence of Xpert MTB/XDR accuracy for detection of resistance to isoniazid and fluoroquinolones in people irrespective of rifampicin resistance and to ethionamide and amikacin in people with known rifampicin resistance, reflecting real-world situations. We used pDST, except for ethionamide resistance where we considered gDST a better reference standard.

Main results

We included two multicentre studies from high multidrug-resistant/rifampicin-resistant tuberculosis burden countries, reporting on six independent study cohorts, involving 1228 participants for pulmonary tuberculosis detection and 1141 participants for drug resistance detection. The proportion of participants with rifampicin resistance in the two studies was 47.9% and 80.9%. For tuberculosis detection, we judged high risk of bias for patient selection owing to selective recruitment. For ethionamide resistance detection, we judged high risk of bias for the reference standard, both pDST and gDST, though we considered gDST a better reference standard.

Pulmonary tuberculosis detection

- Xpert MTB/XDR sensitivity range, 98.3% (96.1 to 99.5) to 98.9% (96.2 to 99.9) and specificity range, 22.5% (14.3 to 32.6) to 100.0% (86.3 to 100.0); median prevalence of pulmonary tuberculosis 91.3%, (interquartile range, 89.3% to 91.8%), (2 studies; 1 study reported on 2 cohorts, 1228 participants; very low-certainty evidence, sensitivity and specificity).

Drug resistance detection

People irrespective of rifampicin resistance

- Isoniazid resistance: Xpert MTB/XDR summary sensitivity and specificity (95% confidence interval (CI)) were 94.2% (87.5 to 97.4) and 98.5% (92.6 to 99.7) against pDST, (6 cohorts, 1083 participants, moderate-certainty evidence, sensitivity and specificity).

- Fluoroquinolone resistance: Xpert MTB/XDR summary sensitivity and specificity were 93.2% (88.1 to 96.2) and 98.0% (90.8 to 99.6) against pDST, (6 cohorts, 1021 participants; high-certainty evidence, sensitivity; moderate-certainty evidence, specificity).

People with known rifampicin resistance

- Ethionamide resistance: Xpert MTB/XDR summary sensitivity and specificity were 98.0% (74.2 to 99.9) and 99.7% (83.5 to 100.0) against gDST, (4 cohorts, 434 participants; very low-certainty evidence, sensitivity and specificity).

- Amikacin resistance: Xpert MTB/XDR summary sensitivity and specificity were 86.1% (75.0 to 92.7) and 98.9% (93.0 to 99.8) against pDST, (4 cohorts, 490 participants; low-certainty evidence, sensitivity; high-certainty evidence, specificity).

Of 1000 people with pulmonary tuberculosis, detected as tuberculosis by Xpert MTB/XDR:

- where 50 have isoniazid resistance, 61 would have an Xpert MTB/XDR result indicating isoniazid resistance: of these, 14/61 (23%) would not have isoniazid resistance (FP); 939 (of 1000 people) would have a result indicating the absence of isoniazid resistance: of these, 3/939 (0%) would have isoniazid resistance (FN).

- where 50 have fluoroquinolone resistance, 66 would have an Xpert MTB/XDR result indicating fluoroquinolone resistance: of these, 19/66 (29%) would not have fluoroquinolone resistance (FP); 934 would have a result indicating the absence of fluoroquinolone resistance: of these, 3/934 (0%) would have fluoroquinolone resistance (FN).

- where 300 have ethionamide resistance, 296 would have an Xpert MTB/XDR result indicating ethionamide resistance: of these, 2/296 (1%) would not have ethionamide resistance (FP); 704 would have a result indicating the absence of ethionamide resistance: of these, 6/704 (1%) would have ethionamide resistance (FN).

- where 135 have amikacin resistance, 126 would have an Xpert MTB/XDR result indicating amikacin resistance: of these, 10/126 (8%) would not have amikacin resistance (FP); 874 would have a result indicating the absence of amikacin resistance: of these, 19/874 (2%) would have amikacin resistance (FN).

Authors' conclusions

Review findings suggest that, in people determined by Xpert MTB/XDR to be tuberculosis-positive, Xpert MTB/XDR provides accurate results for detection of isoniazid and fluoroquinolone resistance and can assist with selection of an optimised treatment regimen. Given that Xpert

MTB/XDR targets a limited number of resistance variants in specific genes, the test may perform differently in different settings. Findings in this review should be interpreted with caution. Sensitivity for detection of ethionamide resistance was based only on Xpert MTB/XDR detection of mutations in the *inhA* promoter region, a known limitation. High risk of bias limits our confidence in Xpert MTB/XDR accuracy for pulmonary tuberculosis.

Xpert MTB/XDR's impact will depend on its ability to detect tuberculosis (required for DST), prevalence of resistance to a given drug, health care infrastructure, and access to other tests.

PLAIN LANGUAGE SUMMARY

Xpert MTB/XDR, a rapid test for resistance to tuberculosis drugs

Why is improving the diagnosis of tuberculosis drug resistance important?

Tuberculosis tests, like Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Truenat, only diagnose rifampicin resistance, but do not provide information about resistance to other drugs used to treat tuberculosis. This information is needed to allow for effective treatment to be started quickly.

Not recognizing tuberculosis drug resistance when present (false negative, FN) may result in severe illness and death. An incorrect diagnosis of tuberculosis drug resistance (false positive, FP) may result in stigma and prolonged and unnecessary treatment with less effective drugs that have more side effects.

What is the aim of this review?

How accurate is Xpert MTB/XDR for detecting pulmonary tuberculosis and resistance to tuberculosis drugs (i.e. isoniazid, fluoroquinolones, ethionamide, and amikacin) in adults?

What was studied in the review?

Xpert MTB/XDR is a rapid test for detecting tuberculosis and drug resistance in one test, suitable for laboratories that do not require advanced skills and infrastructure. We assessed Xpert MTB/XDR accuracy against three reference standards.

What are the main results of the review?

We identified two multicentre studies reporting on six separate cohorts (groups of study participants), 1228 participants for pulmonary tuberculosis detection and 1141 participants for drug resistance detection.

For pulmonary tuberculosis detection, we included two studies (one reporting on two separate cohorts). We did not determine an overall summary of Xpert MTB/XDR accuracy.

If Xpert MTB/XDR were to be used in 1000 people with suspected tuberculosis of whom 100 have tuberculosis:

- an estimated 98 to 99 people would have an Xpert MTB/XDR result indicating tuberculosis: of these 1 to 2 (1%) would not have tuberculosis (FP); and 203 to 900 people would have a result indicating the absence of tuberculosis: of these 0 to 697 (0% to 77%) would have tuberculosis (FN).

Drug resistance detection

Of 1000 people detected as tuberculosis positive by Xpert MTB/XDR:

- where 50 have isoniazid resistance, an estimated 61 would have an Xpert MTB/XDR result indicating isoniazid resistance: of these, 14/61 (23%) would not have isoniazid resistance (FP); and 939 (of the 1000 people) would have an Xpert MTB/XDR result indicating the absence of isoniazid resistance: of these, 3/939 (0%) would have isoniazid resistance (FN);

- where 50 have isoniazid resistance, 61 (of 1000 people) would have an Xpert MTB/XDR result indicating isoniazid resistance: of these, 14/61 (23%) would not have isoniazid resistance (FP); and 939 (of 1000 people) would have a result indicating the absence of isoniazid resistance: of these, 3/939 (0%) would have isoniazid resistance (FN);

- where 50 have fluoroquinolone resistance, 66 would have an Xpert MTB/XDR result indicating fluoroquinolone resistance: of these, 19/66 (29%) would not have fluoroquinolone resistance (FP); and 934 would have a result indicating the absence of fluoroquinolone resistance: of these, 3/934 (0%) would have fluoroquinolone resistance (FN);

- where 300 have ethionamide resistance, 296 would have an Xpert MTB/XDR result indicating ethionamide resistance: of these, 2/296 (1%) would not have ethionamide resistance (FP); and 704 would have a result indicating the absence of ethionamide resistance: of these, 6/704 (1%) would have ethionamide resistance (FN);

- where 135 have amikacin resistance, 126 would have an Xpert MTB/XDR result indicating amikacin resistance: of these, 10/126 (8%) would not have amikacin resistance (FP); and 874 would have a result indicating the absence of amikacin resistance: of these, 19/874 (2%) would have amikacin resistance (FN).

How reliable are the results of the studies in this review?

For pulmonary tuberculosis detection, we did not consider the results reliable because around 90% of the participants had Xpert-detected pulmonary tuberculosis to begin with due to the way people were chosen to participate in the studies. For drug resistance detection, we were confident in the results, except for results for ethionamide resistance detection, where the reference standards were not ideal.

Who do the results of this review apply to?

People with suspected pulmonary tuberculosis and tuberculosis drug resistance living in countries with a high burden of tuberculosis drug resistance.

How up-to-date is this review?

We searched for studies up to 23 September 2021. Searches were limited to 2015 onwards as Xpert MTB/XDR was launched in July 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table, Xpert MTB/XDR for pulmonary tuberculosis

Review question: what is the diagnostic accuracy of Xpert MTB/XDR for detection of pulmonary tuberculosis?

Population: people with presumptive pulmonary tuberculosis
Role: an initial test
Index test: Xpert MTB/XDR
Threshold for index test: an automated result is provided
Reference standard: solid or liquid culture
Studies: cross-sectional
Setting: the intended use setting is peripheral and intermediate level laboratories

Limitations: selective recruitment of participants could lead to sensitivity being overestimated; participants may have been on tuberculosis treatment, which could lead to specificity being underestimated. In one study, data were not reported separately for the independent study cohorts. Owing to heterogeneity in both the characteristics of participants and observed specificity values, we did not perform a meta-analysis. We had limited data to assess the number of people with tuberculosis who were missed (not detected as tuberculosis-positive by Xpert MTB/XDR to begin with) and would have drug susceptibility results uncharacterised by Xpert MTB/XDR

Xpert MTB/XDR sensitivity range 98.3% to 98.9%: specificity range 22.5% to 100.0%

Test result	**Number of results per 1000 people tested (95% CI)**			**№ of participants (studies, study cohorts)**	**Certainty of the evidence (GRADE)**
	Prevalence 2.5%	**Prevalence 10%**	**Prevalence 30%**		
True positives people with pulmonary tuberculosis	25 to 25	98 to 99	295 to 297	799 (2 studies of which 1 reported on 2 study cohorts)	⊕○○○ VERY LOW[a,b]
False negatives people incorrectly classified as not having pulmonary tuberculosis	0 to 0	1 to 2	3 to 5		
True negatives people without pulmonary tuberculosis	219 to 975	203 to 900	158 to 700	429 (2 studies of which 1 reported on 2 study cohorts)	⊕○○○ VERY LOW[b,c,d]
False positives people incorrectly classified as having pulmonary tuberculosis	0 to 756	0 to 697	0 to 542		

Abbreviations: **CI:** confidence interval; **№:** number.
Prevalence values in the table were suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of pulmonary tuberculosis was 91.3%, interquartile range, 89.3% to 91.8%.
[a]We downgraded two levels for risk of bias for selective recruitment of participants.

[b]We noted important differences between the review question and the populations studied including prior testing with Xpert MTB/RIF and Xpert Ultra. The median prevalence in the included studies was not within the range of the three prevalence values provided in the Summary of findings table. We downgraded one level for indirectness.
[c]For individual studies, specificity estimates ranged from 22% to 99%. We could in part explain the low specificity in one study by the small number of non-tuberculosis cases and that participants may have been receiving tuberculosis treatment (participants may have tested Xpert MTB/XDR positive and culture (reference standard) negative and be classified as false-positive). We downgraded one level for inconsistency.
[d]We thought the range provided for true negatives and false positives would likely lead to different clinical decisions depending on which values were assumed. We downgraded one level for imprecision.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 2. Summary of findings table, Xpert MTB/XDR for isoniazid resistance

Review question: what is the diagnostic accuracy of Xpert MTB/XDR for detection of isoniazid resistance?
Population: adults with pulmonary tuberculosis irrespective of rifampicin resistance (i.e. whether or not their rifampicin resistance status was known), detected as tuberculosis positive by Xpert MTB/XDR

Index test: Xpert MTB/XDR

Role: an initial test

Xpert MTB/XDR must first detect tuberculosis (even if the patient is already tuberculosis-positive by another test) before it can detect a resistant or susceptible result
Threshold for index test: an automated result is provided
Prior tests: before receiving Xpert MTB/XDR, people typically will have received testing with another WHO-recommended rapid diagnostic test to confirm tuberculosis

Reference standard: culture-based phenotypic drug susceptibility testing
Studies: cross-sectional
Setting: the intended use setting is peripheral and intermediate level laboratories

Limitations: although the population is adults with pulmonary tuberculosis irrespective of rifampicin resistance, we note that most participants had rifampicin resistance

Xpert MTB/XDR summary sensitivity 94.2% (87.5 to 97.4) and specificity 98.5% (92.6 to 99.7)

Test result	Number of results per 1000 people tested (95% CI)			№ of participants (studies, study cohorts)	Certainty of the evidence (GRADE)
	Prevalence 1%	Prevalence 5%	Prevalence 10%		
True positives people with isoniazid resistance	9 (9 to 10)	47 (44 to 49)	94 (88 to 97)	756 (2 studies reporting on 6 study cohorts)	⊕⊕⊕◯ MODERATE[a,b]
False negatives	1 (0 to 1)	3 (1 to 6)	6 (3 to 12)		

people incorrectly classified as not having isoniazid resistance					
True negatives people without isoniazid resistance	975 (917 to 987)	936 (880 to 947)	887 (833 to 897)	327 (2 studies reporting on 6 study cohorts)	⊕⊕⊕◯ MODERATE[a,b]
False positives people incorrectly classified as having isoniazid resistance	15 (3 to 73)	14 (3 to 70)	13 (3 to 67)		

Abbreviations: **CI:** confidence interval; **№:** number.
Prevalence values in the table were suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of isoniazid resistance in the six study cohorts was 67.6%, interquartile range, 63.1% to 78.1%,
[a]We had several concerns about whether there was indirectness in the populations studied. First, the median prevalence of isoniazid resistance in this analysis was 67.6%, 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 multidrug-resistant strains. That is, there are studies that suggest that a more diverse set of mutations can be found in mono-resistant strains than multidrug-resistant strains. Third, although the population for this PICO question is 'irrespective of rifampicin resistance,' owing to enrolment criteria, most participants were rifampicin resistant. We downgraded one level for indirectness.
[b]Sensitivity estimates ranged from 81% (New Delhi) to 99% (Mubai and Moldova). Regarding the low sensitivity estimate in New Delhi, heteroresistance and resistance mechanisms outside of those detectable by the Xpert MTB/XDR at this site may in part explain the low sensitivity. We did not downgrade for inconsistency.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 3. Summary of findings table, Xpert MTB/XDR for fluoroquinolone resistance

Review question: what is the diagnostic accuracy of Xpert MTB/XDR for detection of fluoroquinolone resistance?
Population: adults with pulmonary tuberculosis irrespective of rifampicin resistance (i.e. whether or not their rifampicin resistance status was known), detected as tuberculosis positive by Xpert MTB/XDR

Index test: Xpert MTB/XDR

Role: an initial test

Xpert MTB/XDR must first detect tuberculosis (even if the patient is already tuberculosis-positive by another test) before it can detect a resistant or susceptible result
Threshold for index test: an automated result is provided
Prior tests: before receiving Xpert MTB/XDR, people typically will have received testing with another WHO-recommended rapid diagnostic test to confirm tuberculosis

Reference standard: culture-based phenotypic drug susceptibility testing
Study design: cross-sectional
Setting: the intended use setting is peripheral and intermediate level laboratories

Limitations: Although the population is adults with pulmonary tuberculosis irrespective of rifampicin resistance, we note that most participants had rifampicin resistance
Xpert MTB/XDR sensitivity 93.2% (88.1 to 96.2) and specificity 98.0% (90.8 to 99.6)

Test result	Number of results per 1000 people tested (95% CI)			№ of participants (studies, study cohorts)	Certainty of the evidence (GRADE)
	Prevalence 1%	Prevalence 5%	Prevalence 10%		
True positives people with fluoroquinolone resistance	9 (9 to 10)	47 (44 to 48)	93 (88 to 96)	381 (2 studies reporting on 6 study cohorts)	⊕⊕⊕◯ HIGH[a,b]
False negatives people incorrectly classified as not having fluoroquinolone resistance	1 (0 to 1)	3 (2 to 6)	7 (4 to 12)		
True negatives people without fluoroquinolone resistance	970 (899 to 986)	931 (863 to 946)	882 (817 to 896)	640 (2 studies reporting on 6 study cohorts)	⊕⊕⊕◯ MODERATE[a,c]
False positives people incorrectly classified as having fluoroquinolone resistance	20 (4 to 91)	19 (4 to 87)	18 (4 to 83)		

Abbreviations:**CI:** confidence interval; **№:** number.
Prevalence values in the table were suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of fluoroquinolone resistance in the six study cohorts was 33.7%, interquartile range, 25.2% to 48.2%.

[a]All study cohorts were conducted in high multidrug-resistant/rifampicin-resistant tuberculosis burden countries. The median prevalence of fluoroquinolone resistance in the study cohorts was 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 question is 'irrespective of rifampicin resistance', we note that most participants had known rifampicin resistance. We did not downgrade for indirectness. This was a judgement.

[b]Sensitivity estimates ranged from 83% (New Delhi) to 98% (Mumbai). Except for New Delhi, sensitivity was ≥ 91%. Regarding the low sensitivity estimate in New Delhi, heteroresistance and rare mutations at this site may in part explain the low sensitivity. We did not downgrade for inconsistency.

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

GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 4. Summary of findings table, Xpert MTB/XDR for ethionamide resistance

Review question: what is the diagnostic accuracy of Xpert MTB/XDR for detection of ethionamide resistance?
Population: adults with pulmonary tuberculosis with known rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR

Role: an initial test
Index test: Xpert MTB/XDR

Xpert MTB/XDR must first detect tuberculosis (even if the patient is already tuberculosis-positive by another test) before it can detect a resistant or susceptible result
Threshold for index test: an automated result is provided
Prior tests: before receiving Xpert MTB/XDR, people typically will have received testing with another WHO-recommended rapid diagnostic test to confirm tuberculosis

Reference standard: genotypic drug susceptibility testing
Study design: cross-sectional
Setting: the intended use setting is peripheral and intermediate level laboratories

Limitations: not all of the loci (i.e. *ethA*, *ethR*, and *inhA* promoter) required for the reference standard to correctly classify the target condition were included
Xpert MTB/XDR sensitivity 98.0% (74.2 to 99.9) and specificity 99.7% (83.5 to 100.0)

Test result	**Number of results per 1000 people tested (95% CI)**			**№ of participants (studies, study cohorts)**	**Certainty of the evidence (GRADE)**
	Prevalence 20%	**Prevalence 30%**	**Prevalence 50%**		
True positives people with ethionamide resistance	196 (148 to 200)	294 (223 to 300)	490 (371 to 500)	167 (1 study reporting on 4 study cohorts)	⊕◯◯◯ VERY LOW [a,b,c]
False negatives people incorrectly classified as not having ethionamide resistance	4 (0 to 52)	6 (0 to 77)	10 (0 to 129)		
True negatives people without ethionamide resistance	798 (668 to 800)	698 (584 to 700)	499 (418 to 500)	267 (1 study reporting on 4 study cohorts)	⊕◯◯◯ VERY LOW [a,b,d]
False positives people incorrectly classified as having ethionamide resistance	2 (0 to 132)	2 (0 to 116)	1 (0 to 82)		

Abbreviations: **CI:** confidence interval; **№:** number.
Prevalence values in the table were suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of ethionamide resistance in the four study cohorts was 39.3%, interquartile range, 25.4% to 52.3%.
[a]We thought there was very serious risk of bias in the reference standard domain because of the absence of several loci (i.e. *ethA*, *ethR*, and *inhA* promoter) required for the reference standard to correctly classify the target condition. Of note, against a phenotypic drug susceptibility reference standard, which does not have this limitation, the summary sensitivity estimate was considerably lower at 51.7% (33.1 to 69.8). We downgraded two levels for risk of bias.
[b]Sensitivity estimates ranged from 78% to 100%. The heterogeneity could be explained in part by the small number of resistant cases in New Delhi and South Africa. We did not downgrade for inconsistency.
[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. We downgraded one level for imprecision.
[d]The 95% CI was wide. 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.
GRADE certainty of the evidence

High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 5. Summary of findings table, Xpert MTB/XDR for amikacin resistance

Review question: what is the diagnostic accuracy of Xpert MTB/XDR for detection of amikacin resistance?
Population: adults with pulmonary tuberculosis with known rifampicin resistance, detected as tuberculosis-positive by Xpert MTB/XDR

Index test: Xpert MTB/XDR

Role: an initial test

Xpert MTB/XDR must first detect tuberculosis (even if the patient is already tuberculosis-positive by another test) before it can detect a resistant or susceptible result
Threshold for index test: an automated result is provided
Prior tests: before receiving Xpert MTB/XDR, people typically will have received testing with another WHO-recommended rapid diagnostic test to confirm tuberculosis

Reference standard: culture-based phenotypic drug susceptibility testing
Studies: cross-sectional
Setting: the intended use setting is peripheral and intermediate level laboratories
Xpert MTB/XDR sensitivity 86.1% (75.0 to 92.7) and specificity 98.9% (93.0 to 99.8)

Test result	Number of results per 1000 people tested (95% CI)			№ of participants (studies, study cohorts)	Certainty of the evidence (GRADE)
	Prevalence 6%	Prevalence 13.5%	Prevalence 20%		
True positives people with amikacin resistance	52 (45 to 56)	116 (101 to 125)	172 (150 to 185)	65 (1 study reporting on 4 study cohorts)	⊕⊕◯◯ LOW[a,b]
False negatives people incorrectly classified as not having amikacin resistance	8 (4 to 15)	19 (10 to 34)	28 (15 to 50)		
True negatives people without amikacin resistance	930 (874 to 938)	855 (804 to 863)	791 (744 to 798)	425 (1 study reporting on 4 study cohorts)	⊕⊕⊕⊕ HIGH
False positives people incorrectly classified as having amikacin resistance	10 (2 to 66)	10 (2 to 61)	9 (2 to 56)		

Abbreviations: **CI:** confidence interval; **№:** number.

Prevalence values in the were table suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of amikacin resistance in the four study cohorts was 13.5%, interquartile range, 9.6% to 21.0%.

[a]Sensitivity estimates were inconsistent, ranging from 75% (New Delhi) to 95% (South Africa), though the 95% CIs overlapped. The heterogeneity could be explained in part by the small number of resistant cases in New Delhi. We did not downgrade for inconsistency.

[b]The 95% CI was wide. There were few participants with amikacin resistance contributing to this analysis for the observed sensitivity. We downgraded two levels for imprecision.

GRADE certainty of the evidence

High: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

BACKGROUND

A glossary of terms related to this Cochrane Review is provided in Appendix 1.

Tuberculosis continues to cause great suffering worldwide. Globally, in 2020, tuberculosis ranked second as the cause of death from a single infectious agent after COVID-19; around 10 million people developed tuberculosis disease; and around 1.5 million people died (WHO Global Tuberculosis Report 2021). The COVID-19 pandemic has had a disastrous effect on all aspects of global health, in particular, on tuberculosis services. According to the World Health Organization (WHO), in 2020, case notifications decreased by 18% compared to 2019 and, for the first time in over a decade, annual deaths from tuberculosis increased (Pai 2022; WHO Global Tuberculosis Report 2021). People with tuberculosis are often poor and disadvantaged, have more limited access to health care, and often face stigma and discrimination (WHO Global Tuberculosis Report 2021). Under-nourishment, HIV-coinfection, alcohol use disorders, smoking, and diabetes mellitus are risk factors for the development of tuberculosis. Yet when tuberculosis is detected early and effectively treated, the disease is largely curable.

Drug-resistant tuberculosis is a critical public health problem. Multidrug-resistant tuberculosis (MDR-TB, defined below) and extensively drug-resistant tuberculosis (XDR-TB, defined below) are responsible for almost one third of deaths due to antimicrobial resistance globally (O'Neill 2016). In 2019, approximately 0.5 million people developed multidrug-resistant (MDR)/rifampicin-resistant tuberculosis. Of the 465,000 new cases of rifampicin-resistant tuberculosis in 2019, three countries accounted for around one half of the cases: India (27%), China (14%), and the Russian Federation (8%) (WHO Global Tuberculosis Report 2020).

In addition, drug-resistant tuberculosis is impeding progress towards the WHO's End TB targets (WHO End TB 2015), and those in United Nations Sustainable Development Goal 3 (United Nations Sustainable Development Goals 2030). A vital part of the END TB strategy is early diagnosis through universal access to a WHO-recommended rapid diagnostic test and drug susceptibility testing (DST), which determines whether *Mycobacterium tuberculosis* (*M tuberculosis*) bacteria, the causative agent of tuberculosis, are susceptible or resistant to drugs (WHO End TB 2015). This systematic review assessed the diagnostic accuracy of Xpert MTB/XDR, a newly developed nucleic acid amplification test (NAAT) that detects pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin.

Drug-resistant tuberculosis categories

Five categories are used to classify cases of drug-resistant tuberculosis (WHO Consolidated Guidelines (Module 4) 2020; WHO Extensively Drug-Resistant Tuberculosis 2021).

1. Rifampicin-resistant tuberculosis is caused by *M tuberculosis* strains resistant to rifampicin (resistance caused by mutations in a small region of the *rpoB* gene). These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or to other drugs.
2. MDR-TB is tuberculosis caused by resistance to at least rifampicin and isoniazid, two core tuberculosis drugs. A subset of people with rifampicin-resistant tuberculosis will have MDR-TB.
3. Isoniazid-resistant tuberculosis is caused by *M tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.
4. Pre-XDR-TB is caused by *M tuberculosis* that fulfils the definition of MDR-TB or rifampicin-resistant tuberculosis, and which are also resistant to a fluoroquinolone. Fluoroquinolones include levofloxacin and moxifloxacin.
5. XDR-TB is caused by *M tuberculosis* that fulfils the definition of rifampicin-resistant or MDR-TB and which are also resistant to a fluoroquinolone and at least one other additional Group A drug (bedaquiline, linezolid). The present version of Xpert MTB/XDR is not capable of detecting WHO-defined XDR-TB owing to an update in the definition to take into consideration new and repurposed drugs for tuberculosis treatment.

MDR/rifampicin-resistant tuberculosis

Rifampicin resistance is already detected by rapid molecular WHO-recommended diagnostic tests (such as Xpert MTB/RIF, Xpert MTB/RIF Ultra, and Truenat assays) that simultaneously detect tuberculosis and rifampicin resistance. These conditions are combined together in a single test because rifampicin resistance is the most frequent form of tuberculosis resistance. Globally in 2020, 69% of bacteriologically confirmed new tuberculosis cases were tested for rifampicin resistance, though testing coverage varied, for example, 58% in Indonesia and 98% in India (WHO Global Tuberculosis Report 2021). And among people with rifampicin resistance, 77,626/157,842 (49.2%) were tested for resistance to any fluoroquinolone (WHO Global Tuberculosis Report 2021).

Isoniazid mono-resistant tuberculosis

In 2019, 13% of new tuberculosis cases and 17% of previously treated tuberculosis cases had isoniazid resistance (WHO Global Tuberculosis Report 2020), yet DST for isoniazid is often only performed in people who are rifampicin resistant. Although in high MDR-TB settings the presence of rifampicin resistance alone has served as a proxy for MDR-TB and the basis for treatment decisions (Liu 2019; Nasiri 2018), emerging data suggest that in some settings, rifampicin DST has suboptimal specificity for MDR-TB. This means that testing for isoniazid resistance is increasingly important. For example, one study in the eastern Democratic Republic of the Congo found one in five people with rifampicin resistance to be isoniazid susceptible when tested using the GenoType MTBDR*plus*, a line probe assay (Bisimwa 2020). And the most recent South African National Survey of Drug Resistance found hotspots of rifampicin mono-resistance, where the prevalence ratio of such cases exceeded that of MDR-TB by up to 30% (NICD 2016).

Conversely, isoniazid resistance in the presence of rifampicin susceptibility (isoniazid mono-resistance) is also increasingly recognized as another emerging threat as it is associated with a three-fold increased risk of poor treatment outcomes and is an important enabler of MDR-TB (Espinal 2000). However, isoniazid resistance would be missed by molecular WHO-recommended diagnostic tests. DST for isoniazid is more complicated than for rifampicin owing to a greater variety of resistance-associated variants (including large deletions) across several genes (e.g. loci in *katG*, *inhA*, and *ahpC*) (WHO Catalogue of Mutations 2021). Information on these mutations may not be routinely available in lower resource settings.

Treatment of tuberculosis

All forms of tuberculosis require treatment with multiple drugs to which bacteria are susceptible to cure tuberculosis and avoid selection of drug resistance (WHO Consolidated Guidelines (Module 3) 2021). For people with drug-susceptible tuberculosis, a four-month rifapentine-based regimen, with and without moxifloxacin (a fluoroquinolone), is advocated as a possible alternative to the current standard six-month regimen (Dorman 2021; WHO Rapid Communication 2021). For people with isoniazid-resistant rifampicin-susceptible tuberculosis, a six-month regimen that includes levofloxacin (a fluoroquinolone) is recommended (WHO Consolidated Guidelines (Module 4) 2020).

The introduction of new and repurposed drugs (bedaquiline, clofazimine, linezolid, pretomanid, delamanid) has revolutionized options for treating multidrug-resistant tuberculosis and additional drug resistance by improving treatment success, shortening treatment, and dispensing with injectable medications. Fluoroquinolones, however, remain an important component of these newer approaches (Churchyard 2019; Conradie 2020; Conradie 2021; Guglielmetti 2021; Médecins Sans Frontières 2021; WHO Consolidated Guidelines (Module 4) 2020). To promote the uptake of all of these new regimens and allow for prompt initiation of appropriate treatment, rapid DST, in particular for fluoroquinolones, is critical. A rapid communication from the WHO Global Tuberculosis Programme describes key changes to the treatment of drug-resistant tuberculosis, including six-month oral regimens for the treatment of MDR/rifampicin-resistant tuberculosis (with or without resistance to fluoroquinolones) and a nine-month oral regimen for the treatment of MDR/rifampicin-resistant tuberculosis. Updated guidance is expected later in 2022 (WHO Rapid Communication 2022).

Target condition being diagnosed

The target conditions are pulmonary tuberculosis and resistance to four tuberculosis drugs: isoniazid, fluoroquinolones, ethionamide, and amikacin.

Pulmonary tuberculosis

Tuberculosis is caused by one of several bacterial species belonging to the *Mycobacterium tuberculosis* (*M tuberculosis)* complex of which the main human pathogen is *M tuberculosis.* Tuberculosis encompasses a dynamic spectrum, from latent infection to subclinical disease to active disease (Pai 2016). Tuberculosis in this review refers to active disease. Tuberculosis most commonly affects the lungs (pulmonary tuberculosis) but may affect any organ or tissue outside of the lungs, such as the brain or spine (extrapulmonary tuberculosis). Signs and symptoms of pulmonary tuberculosis typically include a persistent cough (for at least two weeks), fever, night sweats, weight loss, haemoptysis (coughing up blood), and fatigue, but may also be asymptomatic for prolonged periods of time (Frascella 2021). Tuberculosis is spread from person to person through the air.

Tuberculosis drug resistance

Isoniazid resistance: isoniazid is an important and commonly used first-line drug for tuberculosis. Isoniazid affects mycolic acid (cell wall) synthesis. The drug is taken orally (Curry International Tuberculosis Center 2016; Pai 2016).

Fluoroquinolone resistance: the fluoroquinolones are a class of drugs widely used to treat lower respiratory infections. They are second-line drugs for tuberculosis. Ofloxacin is an earlier generation fluoroquinolone and moxifloxacin, levofloxacin, and gatifloxacin are later generation fluoroquinolones. The fluoroquinolones act by relaxing the supercoiling of DNA strands through inhibition of the enzyme DNA gyrase (Chitra 2020). These drugs are mainly taken orally (Curry International Tuberculosis Center 2016; Pai 2016).

Ethionamide resistance: ethionamide is a second-line drug for tuberculosis in the thioamide drug class. Ethionamide affects mycolic acid synthesis. The drug is taken orally (Curry International Tuberculosis Center 2016; Pai 2016).

Amikacin resistance: amikacin is a second-line drug for tuberculosis in the aminoglycoside drug class, along with kanamycin and capreomycin. These drugs act by inhibiting protein synthesis. Amikacin is mainly administered by intramuscular injection (Curry International Tuberculosis Center 2016; Pai 2016). When a second-line injectable drug is needed in a treatment regimen, amikacin is the preferred drug (WHO Consolidated Guidelines (Module 4) 2020).

In addition to the above drug resistances, Xpert MTB/XDR tests for kanamycin resistance and capreomycin resistance. Kanamycin and capreomycin are less relevant for treating drug-resistant tuberculosis now that an all-oral regimen is recommended. Also, the WHO recommends 'kanamycin and capreomycin are not to be included in the treatment of MDR/rifampicin-resistant tuberculosis in patients on longer regimens' (WHO Consolidated Guidelines (Module 4) 2020), (see Index tests).

Index test(s)

Xpert MTB/XDR (Cepheid, Sunnyvale, USA) is a rapid, automated NAAT of low complexity. In a single test, Xpert MTB/XDR can detect *M tuberculosis* complex (MTBC) DNA and mutations associated with resistance to isoniazid, fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin, gatifloxacin), second-line injectable drugs (amikacin, kanamycin, capreomycin), and ethionamide (Cepheid package insert 2021). Xpert MTB/XDR was designed as a 'reflex test.' In a reflex test, when an initial test result meets predetermined criteria, a second test is performed automatically. According to the manufacturer, Xpert MTB/XDR can be used on unprocessed sputum, concentrated sputum sediments, or MGIT (Mycobacteria Growth Indicator Tube) culture. The manufacturer reports that Xpert MTB/XDR accuracy in fresh and frozen sputum specimens is similar (Cepheid package insert 2021).

NAATs are molecular systems that can detect small quantities of genetic material DNA or ribonucleic acid (RNA)) extracted from micro-organisms, such as *M tuberculosis,* by amplifying regions of DNA or RNA to an amount large enough to study in detail. The key advantage of NAATs is that they are rapid diagnostic tests, potentially providing results in a few hours. A variety of molecular amplification methods are available, of which polymerase chain reaction (PCR) is the most common.

Low complexity refers to a situation where no special infrastructure is required and basic laboratory skills are suitable to run the test. To run Xpert MTB/XDR, an initial manual specimen treatment step is needed in which sample reagent is added to the specimen. Sample reagent helps homogenize the specimen and prepare it for in-cartridge DNA extraction. A 15-minute incubation period with occasional mixing by hand is required for homogenisation to be effective. Subsequently, DNA extraction and PCR procedures are performed within the container linked to the diagnostic platform.

Several advantages of the assay have been described by the manufacturer.

- Faster time to result for detection of drug resistance.
- Results in less than 90 minutes.
- Similar easy-to-use process as Xpert MTB/RIF and Xpert MTB/RIF Ultra.
- Run on existing GeneXpert platforms equipped with 10-colour modules.

The following information comes from the manufacturer's package insert (Cepheid package insert 2021). We note that in the package insert, 'MTB' refers to MTBC.

- Regarding isoniazid, Xpert MTB/XDR bases detection of resistance on mutations in the *katG* and *fabG1* genes, *oxyR - ahpC* intergenic region, and *inhA* promoter region of the MTB genome.
- Regarding fluoroquinolones, Xpert MTB/XDR bases detection of resistance on mutations in the *gyrA* and *gyrB* quinolone resistance determining regions of the MTB genome.
- Regarding ethionamide, Xpert MTB/XDR bases detection of resistance on mutations in the *inhA* promoter region of the MTB genome. In addition, it is noted that 'mutations conferring ethionamide resistance are reported to be present in genomic regions not targeted by the Xpert MTB/XDR assay' (Cepheid package insert 2021). Of interest, Brossier and colleagues found that 22/47 (47%) of ethionamide-resistant clinical isolates had mutations in *ethA*. Hence, the absence of mutations in the *inhA* promoter region does not preclude ethionamide resistance (Brossier 2011). (The manufacturer acknowledges that reporting ethionamide resistance based only on the detection of mutations in the *inhA* promoter region is a known limitation that may limit sensitivity, though specificity may be unaffected).
- Regarding amikacin, Xpert MTB/XDR bases detection of resistance on mutations in the *rrs* region of the MTB genome.

When a second-line injectable drug is needed in a treatment regimen, amikacin is the preferred drug (WHO Consolidated Guidelines (Module 4) 2020). Although we prioritised the most important drug resistances to include based on guidance from the WHO, when a study included data for kanamycin or capreomycin resistance, we also reported Xpert MTB/XDR accuracy for detection of resistance to these drugs.

Interpretation of results for Xpert MTB/XDR

Xpert MTB/XDR can report results as MTB NOT DETECTED or MTB DETECTED. If results are reported as MTB DETECTED, each drug is reported as resistance DETECTED or NOT DETECTED. If results are reported as MTB NOT DETECTED, or INVALID, ERROR, or NO RESULT, then no drug resistance results are reported (Figure 1).

Figure 1. Possible test results for each target in the Xpert MTB/XDR assay. [a]Ethionamide will not provide an indeterminant by assay design. Copyright © [2020] [Cepheid Inc]: reproduced with permission.

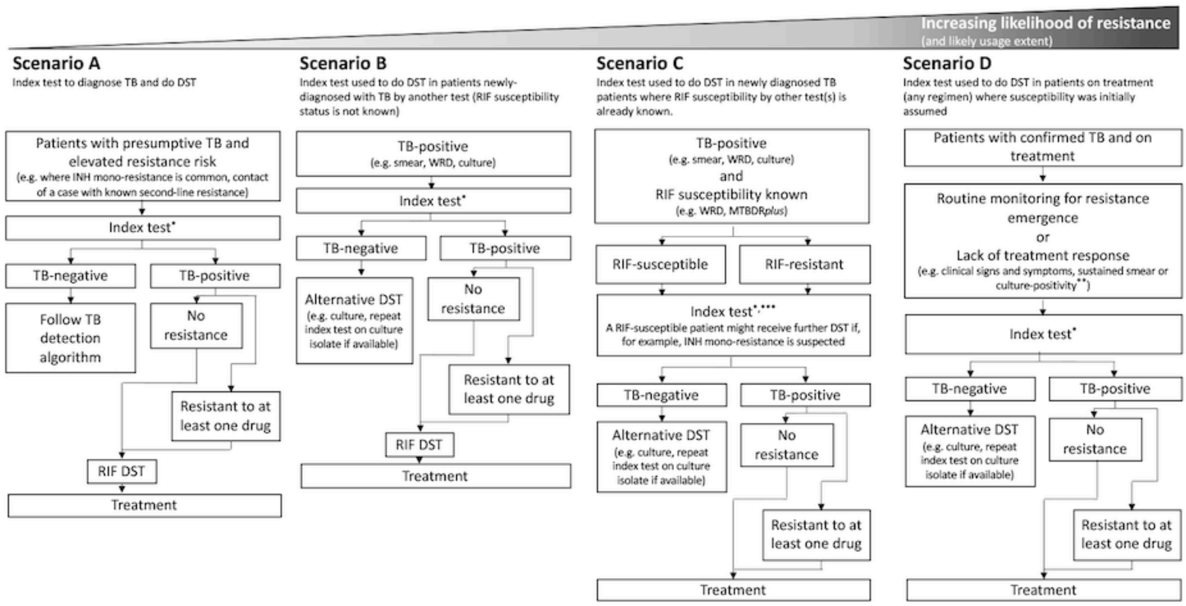
Abbreviations: AMK: amikacin; CAP: capreomycin; ETH: ethionamide; FLQ: fluoroquinolone; INH: isoniazid; KAN: kanamycin; MTB: *Mycobacterium tuberculosis*.

Drug Class	Result Call
N/A	INVALID/ERROR/NO RESULT
	MTB DETECTED
	MTB NOT DETECTED
Isoniazid	Low INH Resistance DETECTED
	INH Resistance DETECTED
	INH Resistance NOT DETECTED
	INH Resistance INDETERMINATE
Fluoroquinolone	Low FLQ Resistance DETECTED
	FLQ Resistance DETECTED
	FLQ Resistance NOT DETECTED
	FLQ Resistance INDETERMINATE
Amikacin	AMK Resistance DETECTED
	AMK Resistance NOT DETECTED
	AMK Resistance INDETERMINATE
Kanamycin	KAN Resistance DETECTED
	KAN Resistance NOT DETECTED
	KAN Resistance INDETERMINATE
Capreomycin	CAP Resistance DETECTED
	CAP Resistance NOT DETECTED
	CAP Resistance INDETERMINATE
Ethionamide[a]	ETH Resistance DETECTED
	ETH Resistance NOT DETECTED

Clinical pathway

Figure 2 outlines several scenarios in the clinical pathway for positioning Xpert MTB/XDR.

Figure 2. Clinical pathway for Xpert MTB/XDR (index test). Abbreviations: DST: drug susceptibility testing; INH: isoniazid; RIF: rifampicin; TB: tuberculosis; WRD: WHO-recommended rapid diagnostic. *Direct testing of sputum is preferred; indirect testing (on cultured isolates) could also be done. **Xpert MTB/XDR may be considered in patients who were Xpert MTB/RIF Ultra rifampicin susceptible prior to treatment and transitioned to Xpert MTB/RIF Ultra rifampicin resistant while on treatment. ***Xpert MTB/XDR may be considered in a rifampicin susceptible patient if INH-mono-resistance is suspected. The composition of a TB treatment regimen will depend on other factors, including RIF susceptibility determined by another test. RIF DST can be done before, in parallel, or after Xpert MTB/XDR. For ease of presentation, TB and MTBC are treated equivalently.



- Scenario A. Xpert MTB/XDR used for detection of pulmonary tuberculosis and drug resistance.
- Scenario B. Xpert MTB/XDR used for detection of drug resistance in people newly diagnosed with pulmonary tuberculosis by another test and whose rifampicin susceptibility is unknown.
- Scenario C. Xpert MTB/XDR used for detection of drug resistance in people newly diagnosed with pulmonary tuberculosis and rifampicin resistance by other tests.
- Scenario D. Xpert MTB/XDR used for detection of drug resistance in people being treated for pulmonary tuberculosis. We did not identify studies that assessed this role.

For each scenario, we expected direct testing (whereby Xpert MTB/XDR is tested directly on a sputum specimen) to be favoured over indirect testing (whereby Xpert MTB/XDR is run on an *M tuberculosis* isolate grown from culture); however, indirect testing remains possible if, for example, direct testing initially failed.

The intended use setting is peripheral and intermediate level laboratories.

The downstream consequences of Xpert MTB/XDR testing include the following.

- TP (true positive): people would benefit from rapid diagnosis and early initiation of effective tuberculosis treatment.
- TN (true negative): people would be spared unnecessary treatment and would benefit from reassurance. For drug resistance detection, in particular, people would be more likely to be treated with more effective drugs with fewer adverse events compared to drugs used to treat drug-resistant tuberculosis.
- False positive (FP): people may experience anxiety and stigma, testing for additional drug resistance and associated diagnostic delays, and treatment with less effective drugs that have serious adverse effects. These consequences are likely more severe in people who have a FP result for drug resistance than in people who have a FP result for pulmonary tuberculosis.
- False negative (FN): if there is a FN result for tuberculosis, there will be no further information about drug susceptibility. If there is FN result for drug resistance, people may be ineligible for some treatment regimens. People would be at increased

risk of morbidity and mortality and there would be continued risk of transmission of tuberculosis and possibly drug-resistant tuberculosis in the community.

Prior test(s)

Before receiving Xpert MTB/XDR, people typically will have received testing with a WHO-recommended rapid diagnostic test to confirm tuberculosis.

Role of index test(s)

The WHO recommends the role of Xpert MTB/XDR as a follow-on test after tuberculosis is confirmed. In this role, Xpert MTB/XDR would be a replacement for line probe assays or culture-based phenotypic DST (pDST). In addition, Xpert MTB/XDR could be used in combination with existing tools that only test for rifampicin resistance, allowing detection of isoniazid-resistant, rifampicin-susceptible tuberculosis (WHO Consolidated Guidelines (Module 3) 2021). Xpert MTB/XDR could also be positioned as an initial test for detection of tuberculosis and drug resistance. We note that the timing of DST for rifampicin and other drugs can be before, in parallel, or after Xpert MTB/XDR is performed, Figure 2,

Alternative test(s)

Here we summarize selective alternative testing methods. The report 'Tuberculosis Diagnostics Pipeline Report: Advancing the Next Generation of Tools' describes additional tuberculosis tests and tests in development (Branigan 2021).

Mycobacterial culture is a method used to grow bacteria on nutrient-rich media. Culture-based DST requires growth of *M tuberculosis* in the presence of drugs at a specific concentration that will inhibit the growth of susceptible bacteria or have no impact on growth of resistant bacteria. Culture is a relatively complex and slow procedure. Solid culture typically takes between four to eight weeks for results, and liquid culture, although more sensitive and rapid than solid culture, requires up to six weeks and is more prone to contamination (Chihota 2010). In addition, culture requires specialized laboratories and highly skilled staff, rarely available in high tuberculosis burden countries. Culture is the reference standard for detection of pulmonary tuberculosis and the basis for pDST.

MeltPro kits (Xiamen Zeesan Biotech Co., Ltd., China) are commercially available, low-complexity tests for detection of mutations associated with resistance to rifampicin, isoniazid, fluoroquinolones, and injectable second-line drugs. Several of the available kits are approved by the China Food and Drug Administration for clinical use. MeltPro testing is designed to detect drug resistance on *M tuberculosis*-positive specimens or cultured isolates. MeltPro testing is performed using an all-in-one machine, Sanity 2.0. Manual pipetting is required for sample preparation, whereas the subsequent processes - nucleic acid extraction, sample loading, detection (i.e. real-time PCR), and interpretation of results - are all fully automatic. The detection of drug resistance is based on multicolor melting curve analysis.

Moderate complexity automated NAATs detect tuberculosis and resistance to rifampicin and isoniazid. Four products have been evaluated and recommenced by the WHO: Abbott RealTime MTB and MTB RIF/INH assays (Abbott Laboratories, Abbott Park, USA); the BD MAX MDR-TB assay (Becton, Dickinson and Company, Franklin Lakes, USA), the Hain FluoroType MTBDR assay (Bruker/Hain Lifescience, Nehren, Germany); and the Roche cobas MTB and MTB-RIF/INH assays (Hoffmann-La Roche, Basel, Switzerland). These tests are faster and simpler to perform than pDST and line-probe assays. Following the initial sample preparation step, these tests are mostly automated. The WHO recommends that 'in people with signs and symptoms of pulmonary tuberculosis, moderate complexity automated NAATs may be used on respiratory samples for the detection of pulmonary tuberculosis, and of rifampicin and isoniazid resistance, rather than culture and pDST (Conditional recommendation; moderate-certainty evidence for diagnostic accuracy)'. Moderate complexity automated NAATs are mainly suited for use in laboratory settings in areas with a high workload (i.e. high population density and high prevalence of tuberculosis). These tests require having a system for referring samples and reporting results (WHO Consolidated Guidelines (Module 3) 2021).

Alternative molecular methods for detection of drug resistance also include the commercial line probe assays, a category of genotypic (molecular) tests. Line probe assays include GenoType MTBDR*plus* assay (Bruker-Hain Lifescience, Nehren, Germany), and the Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan) for first-line tuberculosis drugs and GenoType MTBDR*sl* assay (Bruker-Hain Lifescience, Nehren, Germany) for second-line drugs. These methods have considerable advantages over pDST for scaling up programmatic management and surveillance of drug-resistant tuberculosis, offering speed of diagnosis (one or two days), standardized testing, potential for high through-put, and fewer requirements for laboratory biosafety. Drawbacks are that line probe assays require skills and infrastructure only available in intermediate and central laboratories (WHO Operational handbook - diagnosis 2021).

Rationale

Based on new evidence on the management of drug-resistant tuberculosis, the WHO has issued recommendations that all people with MDR/rifampicin-resistant tuberculosis, including those who are also resistant to fluoroquinolones, may benefit from all-oral treatment regimens (WHO Consolidated Guidelines (Module 4) 2020). In people with tuberculosis and rifampicin-resistant tuberculosis it is critically important to perform additional resistance testing to at least isoniazid and the fluoroquinolones in order to guide treatment decisions. People with isoniazid mono-resistant tuberculosis may also benefit from modified regimens that include fluoroquinolones. Information on *inhA* promotor mutations could also guide high-dose isoniazid therapy. Hence, rapid extended profiling of drug resistance could allow for early initiation of appropriate treatment and likely better patient outcomes. Amplification of drug resistance would also be less likely. Extended profiling of drug resistance could also be of importance in considering the use of the four-month fluoroquinolone-containing regimens for drug-susceptible tuberculosis (Dorman 2021). An all-in-one rapid test to detect resistance to rifampicin and other drugs would be ideal; however, this technology is not currently available.

Xpert MTB/XDR is one assay in a new class of diagnostic tests referred to as 'low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-tuberculosis agents' (WHO Consolidated Guidelines (Module 3) 2021). In 2020, we performed a systematic review to inform updated WHO guidelines on the use of NAATs (including Xpert MTB/XDR) to detect tuberculosis and drug-resistant tuberculosis (WHO Consolidated Guidelines (Module 3) 2021). This Cochrane Review expands on these efforts.

A complementary Cochrane qualitative evidence synthesis addressed the question, 'What are the perspectives and experiences of people providing and receiving low complexity NAATs to diagnose tuberculosis and tuberculosis drug resistance?' In answering this question, the review authors aimed to identify the implications for health equity and effective implementation of the tests (Engel 2022).

OBJECTIVES

- To assess the diagnostic accuracy of Xpert MTB/XDR for pulmonary tuberculosis in people with presumptive pulmonary tuberculosis.
- To assess the diagnostic accuracy of Xpert MTB/XDR for resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin in people with tuberculosis detected by Xpert MTB/XDR, irrespective of rifampicin resistance (whether or not their rifampicin resistance status was known) and with known rifampicin resistance.

Presumptive tuberculosis refers to an individual who presents with symptoms or signs suggestive of tuberculosis (WHO Definitions and Reporting 2020). Symptoms suggestive of tuberculosis include cough, fever, weight loss, and night sweats.

Secondary objectives

As a secondary objective, we planned to compare the diagnostic accuracy of Xpert MTB/XDR by direct testing (whereby Xpert MTB/XDR is tested directly on a sputum specimen) versus indirect testing (whereby Xpert MTB/XDR is performed on a *Mycobacterium tuberculosis* (*M tuberculosis*) isolate grown from culture). However, owing to limited data, we narratively described these analyses and presented results in forest plots.

Investigations of sources of heterogeneity

We planned to investigate the effects of a number of potential sources of heterogeneity as outlined in our protocol, however, our ability to investigate these was limited by the available data. The sources of heterogeneity that we investigated were smear status (pulmonary tuberculosis detection) and type of reference standard, smear status, HIV status, and previous tuberculosis treatment (drug resistance detection).

We note that investigations in people previously treated for tuberculosis are important questions for clinical practice and studies have highlighted the challenges in interpreting the related tests, Xpert MTB/RIF (Theron 2016a) and Xpert MTB/RIF Ultra (Mishra 2020).

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional and cohort studies that assessed the diagnostic accuracy of Xpert MTB/XDR for both pulmonary tuberculosis and tuberculosis drug resistance, or tuberculosis drug resistance alone. We included diagnostic accuracy studies in which people with the target condition and people without the target condition were sampled from a single source population (referred to as a single-gate design) (Rutjes 2005). We only included studies that reported data comparing Xpert MTB/XDR to an acceptable reference standard (defined below) from which we could extract or derive TP, FP, FN, and TN values.

Participants

We included adults 15 years and older with presumptive pulmonary tuberculosis. In addition, we included adults with bacteriologically-confirmed pulmonary tuberculosis irrespective of rifampicin resistance (whether or not their rifampicin resistance status was known) and with known rifampicin resistance. We included HIV-positive and HIV-negative people. We included people who, at study enrolment, did not report previous tuberculosis treatment or reported receiving tuberculosis treatment. We included studies that assessed the diagnostic accuracy of Xpert MTB/XDR using sputum (expectorated or induced) consistent with the intended use of the manufacturer, and studies from all types of health facilities and all laboratory levels (peripheral, intermediate, and central) from all countries.

Index tests

The index test was Xpert MTB/XDR. Xpert MTB/XDR tests for drug resistance after testing has identified the presence of *M tuberculosis* in the specimen. Interpretation of results for Xpert MTB/XDR is shown in Figure 1.

Before receiving Xpert MTB/XDR, people will have typically received testing verifying tuberculosis with another WHO-recommended rapid diagnostic test.

Some people detected as having tuberculosis by another WHO-recommended rapid diagnostic test may not be detected as having tuberculosis by Xpert MTB/XDR, We note that in comparison to related Xpert tests that detected tuberculosis, the limit of detection of Xpert MTB/XDR for *M tuberculosis* was 71.9 colony-forming units (CFU)/mL, similar to the limit of detection of Xpert MTB/RIF (86.9 CFU/mL), but above the limit of detection of Xpert MTB/RIF Ultra (15.6 CFU/mL) (Cao 2021; Chakravorty 2017).

Target conditions

The target conditions were pulmonary tuberculosis and resistance to four tuberculosis drugs: isoniazid, fluoroquinolones, ethionamide, and amikacin.

We included pulmonary tuberculosis as a target condition because some users of the Xpert MTB/XDR assay may want to do the test to detect pulmonary tuberculosis, in particular, in areas where isoniazid mono-resistance is also likely.

Reference standards

Detection of pulmonary tuberculosis

The reference standard for detection of pulmonary tuberculosis was solid or liquid culture or both solid and liquid culture.

- The presence of pulmonary tuberculosis was defined as a positive *M tuberculosis* culture.
- The absence of pulmonary tuberculosis was defined as a negative *M tuberculosis* culture.

Detection of tuberculosis drug resistance

We included three reference standards for detection of drug resistance, pDST, gDST, and a composite reference standard. These methods are used to determine whether *M tuberculosis* bacteria are susceptible or resistant to tuberculosis drugs.

- pDST alone.
  - The presence of drug resistance was defined as drug resistance detected by pDST.
  - The absence of drug resistance for a given drug (referred to as being drug susceptible) was defined as drug resistance not detected by pDST.

We considered pDST to be the most suitable reference standard for detection of resistance to isoniazid, fluoroquinolones, and amikacin. pDST is the conventional method for detecting resistance to first- and second-line tuberculosis drugs.

- gDST alone.
  - The presence of drug resistance was defined as drug resistance detected by gDST.
  - The absence of drug resistance was defined as drug resistance not detected by gDST.

We considered gDST to be the most suitable reference standard for ethionamide resistance because there is considerable overlap in the minimum inhibitory concentrations (MICs) of *M tuberculosis* isolates with and without resistance-causing variants and a pDST reference standard might not correctly classify the target condition.

- Composite reference standard.
  - The presence of drug resistance was defined as drug resistance detected by either pDST or gDST.
  - The absence of drug resistance was defined as drug resistance not detected by both pDST and gDST.

The classification rule for the composite reference standard is based on one of the two reference tests (pDST or gDST) being positive for resistance to a given drug. Consequently, it is not necessary to perform a second reference standard test once the result of the first reference standard test is positive (resistant). Hence, the second reference standard test is only necessary in people with a negative (susceptible) or failed test result (e.g. indeterminate, contaminated) on the first reference standard test (Rutjes 2005). The composite reference standard result was considered drug susceptible when pDST reported drug susceptibility and gDST did not detect a drug-associated resistant mutation.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing).

Electronic searches

We searched the following databases up to 23 September 2021, without language restrictions, using the search terms and strategy described in Appendix 2. We limited our searches to 2015 onwards as Xpert MTB/XDR is a newly developed assay, which was launched in July 2020.

- Cochrane Infectious Diseases Group Specialized Register.
- MEDLINE (Ovid).
- Embase (Ovid).
- Science Citation Index – Expanded, Conference Proceedings Citation Index – Science (CPCI-S), and BIOSIS Previews; all three from the Web of Science.
- Scopus (Elsevier).
- Latin American Caribbean Health Sciences Literature (LILACS) (BIREME; lilacs.bvsalud.org/en/).

We also searched ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch), and the International Standard Randomized Controlled Trials Number (ISRCTN) registry (www.isrctn.com/) for trials in progress, and ProQuest Dissertations & Theses A&I for dissertations, using terms for tuberculosis and Xpert MTB/XDR.

Searching other resources

We reviewed reference lists of included articles and any relevant review articles identified through the above methods. We also contacted researchers at the Foundation for Innovative New Diagnostics (FIND), the WHO Global Tuberculosis Programme, the manufacturer, and other experts in the field of tuberculosis diagnostics for information on ongoing and unpublished studies. We reviewed data submitted via the WHO public call.

Data collection and analysis

Selection of studies

We used Covidence to manage the selection of studies (Covidence). Two review authors independently screened titles and abstracts identified from literature searching to identify potentially eligible studies. We retrieved the article of any citation identified by one of the review authors for full-text review. Then, two review authors independently assessed articles for inclusion using predefined inclusion and exclusion criteria. We resolved disagreements by discussion with a third review author. We recorded all studies excluded after full-text assessment and their reasons for exclusion in Characteristics of excluded studies. We illustrated the study selection process in a PRISMA diagram (Page 2021; Salameh 2020).

Data extraction and management

We developed a data extraction form based on experience with a previous Cochrane Review (Theron 2016b; Appendix 3). Two review authors independently extracted data on study design, participants, reference standards, and data required to populate a 2x2 contingency table. When possible, we extracted data for each study cohort within a multicentre study (see Statistical analysis and data synthesis). We resolved any discrepancies by discussion with a third review author. We entered the extracted data into an Excel database on password-protected computers. Data will be secured in the Liverpool School of Tropical Medicine 'Archive' drives of Cochrane Infectious Diseases Group for future review updates.

We extracted the following information.

- Details of study: first author; publication year; country where testing was performed; setting (primary care laboratory, hospital laboratory, reference laboratory); study design; manner of participant selection; number of participants enrolled; number of participants for whom results were available.

- Characteristics of participants: age; HIV status; smear status; previous tuberculosis treatment.
- Target conditions.
- Reference standards.
- Details of specimen: type (such as expectorated or induced sputum or cultured isolate); condition (fresh or frozen).
- Details of the conduction of the assay, whether performed on a sputum specimen (direct testing) or performed on the cultured isolate grown from the patient specimen (indirect testing).
- Details of outcomes: the number of TP, FP, FN, and TN results.
- Whether the WHO-recommended critical drug concentration was used for the pDST reference standard (WHO Critical Concentrations 2018; WHO Critical Concentrations 2021). We used the currently recommended concentration for each drug to classify studies, not the recommended concentration at the time of the study.
- Inconclusive test results.
- QUADAS-2 items.
- Details of industry sponsorship, if applicable.

We classified country income status as low-income, middle-income, or high-income, according to the World Bank List of Economies (World Bank 2020). In addition, we classified 'country' as being high burden or not high burden for tuberculosis, HIV-associated tuberculosis, and MDR/rifampicin-resistant tuberculosis based on the WHO classification for the period 2021–2025 (WHO Global Tuberculosis Report 2021). A country may be classified as high burden for one, two, or all three of the high burden categories.

We followed Cochrane policy, which states that, 'Anyone engaged in writing a Cochrane Review, who has had any involvement in the conduct, analysis, and publication of a study that could be included the review, is restricted in what they can do with those data. They CANNOT determine the overall study inclusion and exclusion criteria; and they CANNOT make study eligibility decisions about, extract data from, carry out the risk of bias assessment for, or perform GRADE assessments of that study'.

Assessment of methodological quality

We used QUADAS-2 to assess methodological quality (Whiting 2011). QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. We assessed all domains for risk of bias and the first three domains for concerns regarding applicability. Two review authors independently completed QUADAS-2 and resolved disagreements through discussion, if needed, with a third review author. We presented the results of this quality assessment in text and figures. The tool tailored to this review is in Appendix 4.

We appraised methodological quality separately for each study cohort within a multicentre study and separately for each target condition. In addition, for drug resistance detection, in the reference standard domain, we considered risk of bias separately for each drug and each reference standard. This allowed us to assess whether the WHO-recommended critical concentration for the drug was used for the pDST reference standard and whether all relevant loci were included in the gDST reference standard.

Statistical analysis and data synthesis

For multicentre studies, we anticipated that there might have been variability in the frequency and types of mutations associated with resistance to a given drug at the different centres. For this reason, we considered each centre as an independent study cohort. We performed meta-analyses at the study cohort level, if data were available to take this approach.

We displayed key study characteristics in Characteristics of included studies. We plotted estimates of the observed sensitivities and specificities in forest plots with 95% confidence intervals (CIs) using Review Manager 5 (Review Manager 2020).

Detection of pulmonary tuberculosis

For detection of pulmonary tuberculosis, we narratively described the analysis and presented results in forest plots. Owing to heterogeneity in both the participant characteristics and observed specificity values, we did not perform a meta-analysis.

Detection of drug resistance

For detection of drug resistance**,** we took the following analytical approach. We stratified the analyses by type of testing (e.g. directly on sputum); population (irrespective of rifampicin resistance or known rifampicin resistance); target condition; and type of reference standard (pDST, gDST, and composite reference standard).

Within each analysis group (e.g. direct, irrespective of rifampicin resistance, isoniazid resistance, pDST), we plotted estimates of the observed sensitivities and specificities for each study cohort in forest plots with 95% CIs using Review Manager 5 (Review Manager 2020). Where adequate data were available, we combined data using meta-analysis by fitting a bivariate random-effects model (Chu 2006; Macaskill 2010; Reitsma 2005), using Stata (Version 14) with the metandi and meqrlogit commands (Stata). In situations with sparse data, we performed meta-analysis where appropriate by reducing the bivariate model to two univariate random-effects logistic regression models by assuming no correlation between sensitivity and specificity (Takwoingi 2017). When we observed little or no heterogeneity on forest plots, and the analyses consequently did not converge, we further simplified the models into fixed-effect models by eliminating the random-effects parameters for sensitivity or specificity, or both sensitivity and specificity (Takwoingi 2017). In situations where all study cohorts in a meta-analysis reported a sensitivity of 100% or specificity of 100%, we used simple pooling by summing the numbers of TPs and total resistant cases to calculate sensitivity or the numbers of TNs and total susceptible cases to calculate specificity, as required. In these situations when needed, we determined 95% CIs using the Newcombe-Wilson method (Newcombe 1998). We required data from at least four study cohorts for meta-analysis.

Regarding the fluoroquinolone drug class, we estimated test accuracy for the drug class as a whole against pDST, meaning that if there were documented resistance to a given fluoroquinolone, this would be interpreted as resistance to the whole fluoroquinolone class. We used this approach because the fluoroquinolones have high cross-resistance owing to variants within the *gyrA* hotspot region (Zignol 2016).

Inconclusive index test results and missed cases

A test result may be uninterpretable when the main diagnostic feature of the test result is invalid, missing, or obstructed (Shinkins 2013). Invalid inconclusive test results are caused by a property intrinsic to the test. Missing results mean no test result has been recorded though the participant ideally should have had a test result and been included in the study.

For Xpert MTB/XDR, the manufacturer defines two types of invalid inconclusive results, non-determinate and indeterminate.

- A *non-determinate* Xpert MTB/XDR test result is one that results in an Error, Invalid, or No Result and can be due to an operator error, instrument, or cartridge issue (Cepheid package insert 2021). Non-determinate Xpert MTB/XDR test results pertain only to the detection of MTBC, not to the detection of drug resistance.

- An *indeterminate* Xpert MTB/XDR test result is one that indicates that resistance to a given drug could not definitively be detected based on the test's algorithm (Cepheid package insert 2021). This means that, based on quality control criteria, the test was unable to confidently report this particular result and the software suppressed the reporting of this. The same cartridge can be indeterminate for one drug but not another. Indeterminate Xpert MTB/XDR test results pertain only to the detection of drug resistance, not to the detection of MTBC.

We excluded non-determinate and indeterminate results from analyses of diagnostic test accuracy. We performed meta-analyses to estimate the summary proportion of non-determinate and indeterminate results using the metaprop command in Stata (Version 14) (Stata).

- Xpert MTB/XDR MTB NOT DETECTED

When data were available, we reported when the index test did not detect tuberculosis to begin with (missed cases), which could result in resistant cases not receiving a result, Appendix 5.

Investigations of heterogeneity

For each target condition, we investigated heterogeneity through visual examination of forest plots of sensitivity and specificity.

Detection of pulmonary tuberculosis

For Xpert MTB/XDR accuracy by smear status, we narratively described these analyses and presented results in forest plots (see Differences between protocol and review).

Detection of drug resistance

For Xpert MTB/XDR accuracy by smear status, HIV status, and previous tuberculosis treatment, we narratively described these analyses and presented results in forest plots (see Differences between protocol and review).

All covariates were categorical.

- Smear status, positive or negative.
- HIV status, positive or negative.
- Previous tuberculosis treatment or no previous tuberculosis treatment.

Sensitivity analyses

For resistance detection for isoniazid and fluoroquinolones in people irrespective of rifampicin resistance, we performed sensitivity analyses by repeating the meta-analyses and excluding the study (reporting on two study cohorts) sponsored by the manufacturer.

For resistance detection for ethionamide and amikacin in people with known rifampicin resistance, we did not perform sensitivity analyses because the main analyses included only one study (reporting on four study cohorts), which was not sponsored by the manufacturer.

Assessment of reporting bias

We did not conduct formal assessment of publication bias using methods such as funnel plots or regression tests, because such techniques have not been helpful for diagnostic test accuracy studies (Macaskill 2010).

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach for diagnostic studies (Balshem 2011; Schünemann 2008; Schünemann 2016). As recommended, we rated the certainty of evidence as high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) based on five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each outcome (i.e. sensitivity and specificity), the certainty of evidence started as high when there were high-quality studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty. If we found a reason for downgrading, we used our judgement to classify the reason as either serious (downgraded by one level) or very serious (downgraded by two levels). At least two review authors discussed judgements and applied GRADE using the following methods (GRADEpro GDT; Schünemann 2020a; Schünemann 2020b).

Risk of bias: we used QUADAS-2 to assess risk of bias.

Indirectness: we assessed indirectness in relation to the population (including disease spectrum), setting, intervention (index test), and outcomes (accuracy measures). We also use prevalence of the target condition as a guide to whether there was indirectness in the population.

Inconsistency: inconsistency can be caused by clinical heterogeneity or methodological heterogeneity, or it may remain unexplained. GRADE recommends downgrading for unexplained inconsistency in sensitivity and specificity estimates. We had planned to carry out pre-specified analyses to investigate potential sources of heterogeneity and downgrade when we could not explain the inconsistency in the accuracy estimates. However, as mentioned above, data were insufficient to carry out most analyses. We looked at the individual point estimates in the forest plots and judged whether they were more or less the same, as well as the 95% CIs to see if they overlapped.

Imprecision: we considered the width of the 95% CI. In addition, we determined projected ranges for two categories of test results that have the most important consequences for patients, the number of FNs and the number of FPs, and made judgements on imprecision from these calculations. Imprecision also depends on the number of participants included to determine sensitivity and specificity. We took note of the uncertainty around point estimates along with the number of participants providing those data. We acknowledge the judgement of imprecision is subjective.

Publication bias: we considered the comprehensiveness of the literature search and outreach to researchers in tuberculosis, the presence of only studies that produce precise estimates of high accuracy despite small sample size, and knowledge about studies that were conducted, but were not published.

We used GRADEpro (GRADEpro GDT) to create summary of findings tables for each target condition.

The summary of findings tables include the following details.

- The review question and its components, population, (prior tests), setting, index test(s), and reference standard.
- Summary estimates of sensitivity and specificity and 95% CIs.
- The number of included studies and participants contributing to the estimates of sensitivity and specificity.
- Prevalences of the target condition with an explanation of why the prevalences have been chosen.
- An assessment of the certainty of the evidence (GRADE).
- Explanations for downgrading, as needed.

Using GRADE, we assessed certainty of evidence of Xpert MTB/XDR accuracy for detection of resistance to isoniazid and fluoroquinolones in people irrespective of rifampicin resistance and ethionamide and amikacin in people with known rifampicin resistance, reflecting real world situations. For detection of resistance to isoniazid, flouroquinolones, and amikacin, we used pDST as the reference standard (WHO TPP 2021). For detection of resistance to ethionamide, we used gDST as the reference standard.

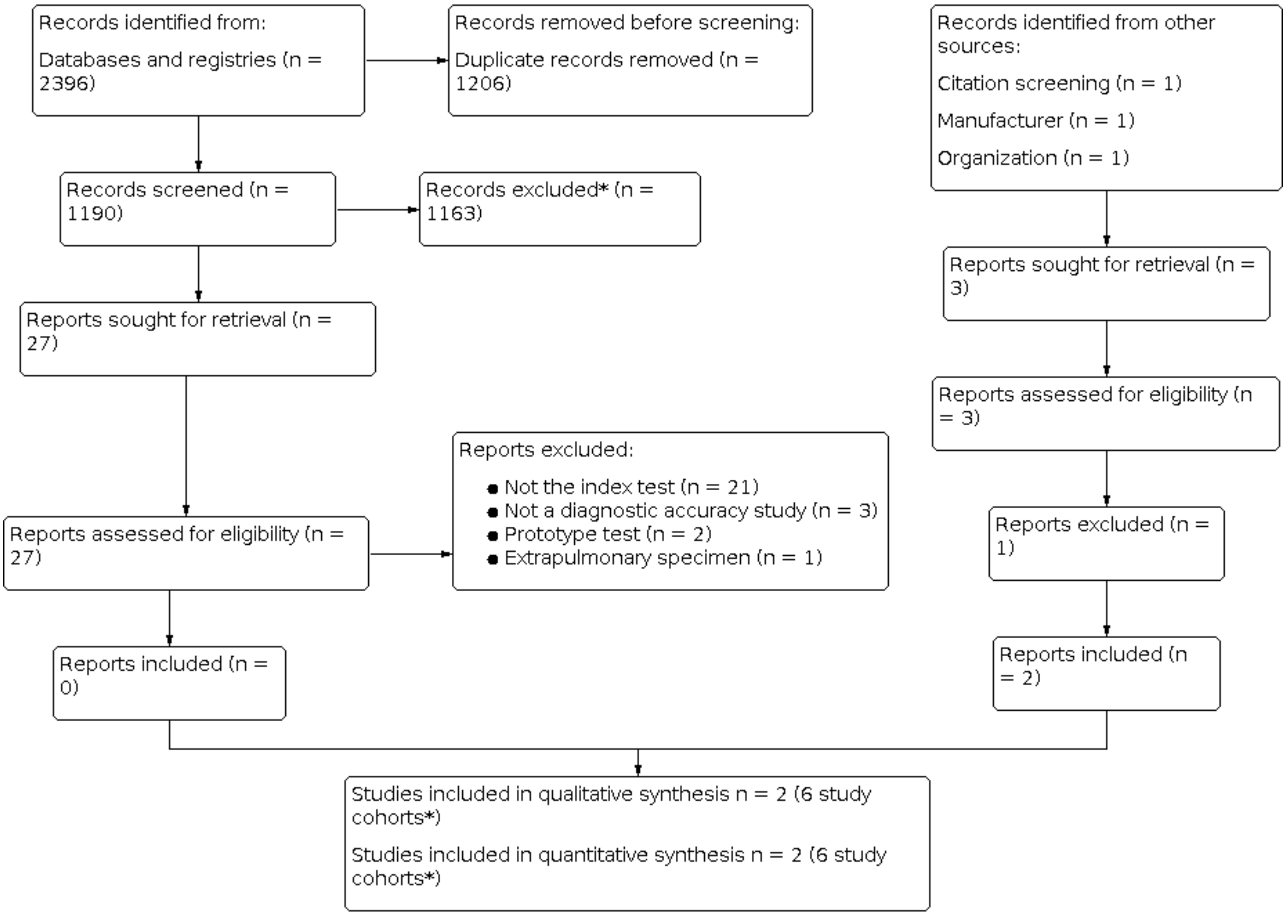
RESULTS

Results of the search

We identified 2396 records from database searching. After removal of 1206 duplicate records, we screened 1190 titles and abstracts for relevance to the review topic. Of these, we excluded 1163 and assessed 27 full-text reports against our inclusion criteria. We excluded all 27 reports for the following reasons: not the index test (n = 21); not a diagnostic accuracy study (n = 3); prototype test (n = 2); and extrapulmonary specimen (n = 1). We identified three records from other sources: one record from the manufacturer (Omar 2020); one record from the Foundation for Innovative New Diagnostics (FIND) (Penn-Nicholson 2021); and one record from additional citation screening (Cao 2021). Following assessment for eligibility, we excluded one report that evaluated Xpert MTB/XDR in both clinical specimens and cultured isolates and the data could not be disaggregated (Cao 2021). Hence, we included two studies reporting on a total of six independent study cohorts. Both studies used a cross-sectional study design. All study cohorts were in high multidrug-resistant/rifampicin-resistant tuberculosis burden countries (Omar 2020; Penn-Nicholson 2021).

Figure 3 shows the PRISMA diagram. We provide a list of excluded studies and reasons for their exclusion in Characteristics of excluded studies.

Figure 3. Study flow diagram. *Two multicentre studies were included, one with two study cohorts and one with four study cohorts. Hence, we included six distinct study cohorts in the review. The following definitions are from Page 2021. Report: a document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information. Record: the title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are "duplicates"; however, records that refer to reports that are merely similar (such as a similar abstract submitted to two different conferences) should be considered unique.



Description of the included studies

See Characteristics of included studies and Table 1.

Omar 2020 was a multicentre study that involved two study cohorts at centres in China (Omar 2020 China) and South Africa (Omar 2020 South Africa). The two study cohorts included a total of 530 participants, of whom 487 (91.9%) had tuberculosis verified by culture and 254 (47.9%) had rifampicin resistance. Xpert MTB/XDR and reference standard testing were performed at a central-level laboratory. Both study cohorts used archived raw sputum or concentrated sputum sediment specimens from participants who had been evaluated for pulmonary tuberculosis in inpatient and outpatient settings. Specimens that were culture positive or negative by LJ (Löwenstein–Jensen) medium or MGIT (Mycobacteria Growth Indicator Tube) were included.

Culture positive specimens were included if they met the following criteria:

- at least 1 mL of frozen sputum sediment or 2 mL of raw sputum was available;
- results were available for smear microscopy and culture (MGIT and/or LJ);
- the specimen had results from Xpert MTB/RIF or Xpert MTB/RIF Ultra testing;
- the specimen had pDST results for isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, and capreomycin; and
- the specimen had gDST results (loci included in the gDST reference standard are listed below).

Culture negative specimens were included if at least 1 mL of frozen sputum sediment or 2 mL of raw sputum was available. Specimens that had previously thawed were excluded.

Penn-Nicholson 2021 was a multicentre study that involved four study cohorts at centres in Mumbai (Penn-Nicholson 2021 India (Mumbai)); Moldova Penn-Nicholson 2021 Moldova); New Delhi

Penn-Nicholson 2021 India (New Delhi); and South Africa (Penn-Nicholson 2021 South Africa). Participants were evaluated for in inpatient and outpatient settings. For detection of pulmonary tuberculosis, of 714 participants initially recruited, 286 (40.1%) reported receiving previous tuberculosis treatment and of 698 participants included in the analysis, 609 (87.2%) had tuberculosis verified by culture. Of 611 participants who had both Xpert MTB/XDR and reference standard results for any drug resistance, 494 (80.9%) had rifampicin resistance. Xpert MTB/XDR and reference standard testing were performed at a central-level laboratory.

The study enrolled participants who had symptoms suggestive of pulmonary tuberculosis (i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis) and a risk factor for drug-resistant tuberculosis as follows:

- previously received greater than one month of treatment for a prior tuberculosis episode; or
- failing tuberculosis treatment with positive sputum smear or culture after ≥ three months of a standard tuberculosis treatment; or
- had close contact with a known drug-resistant tuberculosis case; or
- newly diagnosed with MDR-TB within the last 30 days; or
- previously diagnosed with MDR-TB and failed tuberculosis treatment with a positive sputum smear or culture after ≥ three months of a standard MDR-TB treatment regimen.

Participants received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those with a positive Xpert MTB/RIF or Xpert MTB/RIF Ultra result and a clear rifampicin result (resistant or susceptible) were included. Culture-positive samples were tested by pDST (MGIT) for resistance to isoniazid, rifampicin, fluoroquinolones, ethionamide, amikacin, kanamycin, and capreomycin. Participants were also required to produce an adequate quantity (3 mL) of sputum.

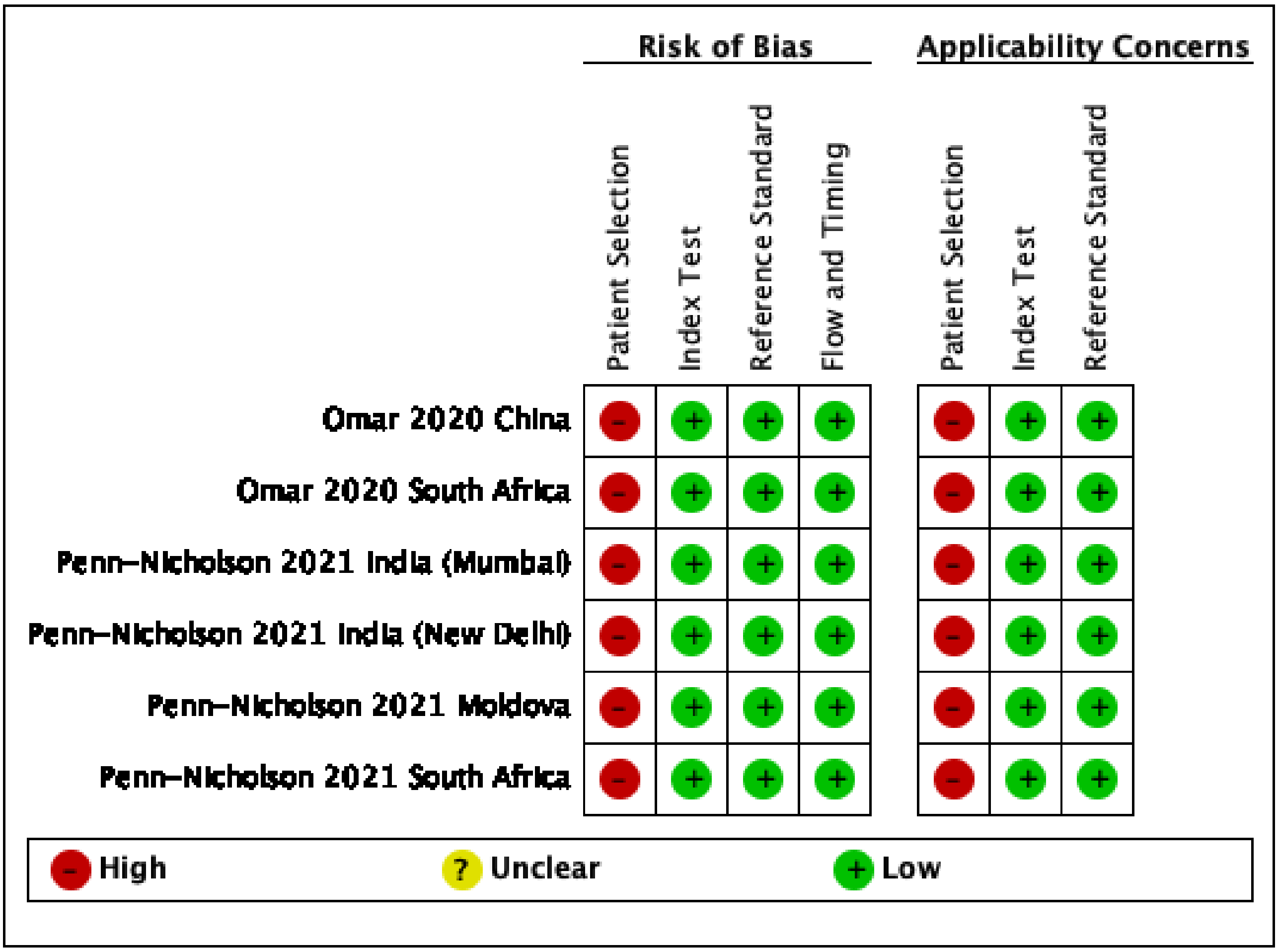
For detection of drug resistance, both multicentre studies evaluated Xpert MTB/XDR against all three reference standards (i.e. pDST, gDST, and composite reference standard). Both multicentre studies included identical loci in the gDST reference standard: *katG*, *inhA* promoter, *fabG1*, *ahpC-oxyR* intergenic region, *gyrA*, *gyrB*, *rrs*, and *eis* promoter.

Methodological quality of included studies

Detection of pulmonary tuberculosis

See Figure 4.

Figure 4. Xpert MTB/XDR for detection of pulmonary tuberculosis. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



In the patient selection domain, we considered all study cohorts (100%) to have high risk of bias. The high proportion of people with tuberculosis (verified by culture), 91.3% in Omar 2020 China, and 92.2% in Omar 2020 South Africasuggested selective recruitment of participants. In Penn-Nicholson 2021 India (Mumbai),Penn-Nicholson 2021 India (New Delhi),Penn-Nicholson 2021 Moldova, and Penn-Nicholson 2021 South Africa), 80.9% of participants had known rifampicin resistance. Regarding applicability for patient selection, we considered all study cohorts to have high concern as the included patients did not match the review question.

In the index test domain, we considered all study cohorts to have low risk of bias and low concern about applicability.

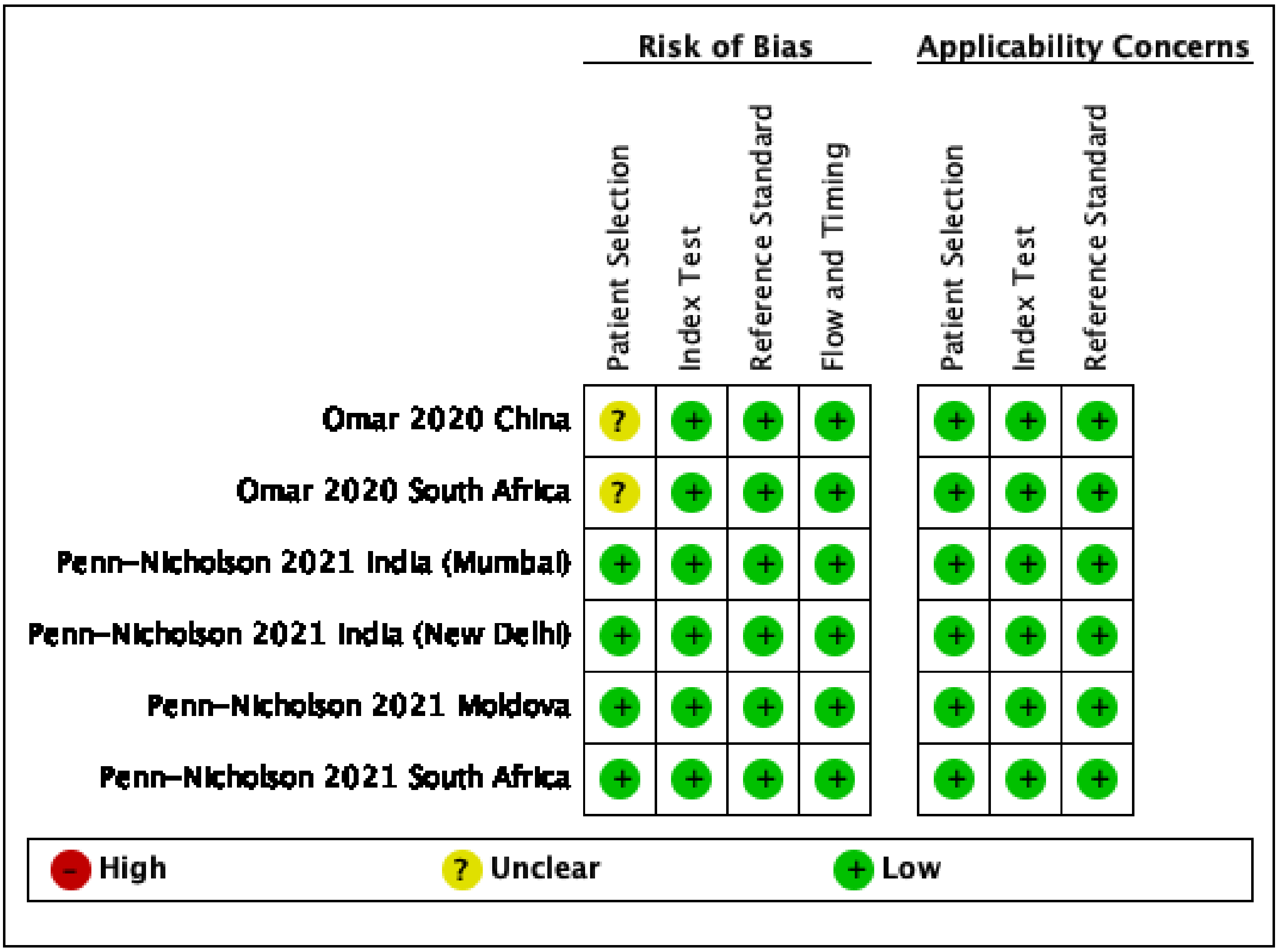
In the reference standard domain, we considered all study cohorts to have low risk of bias and low concern about applicability.

In the flow and timing domain, we considered all study cohorts to have low risk of bias.

Detection of tuberculosis drug resistance

Resitance to isoniazid, fluoroquinolones, and amikacin, Figure 5.

Figure 5. Xpert MTB/XDR for detection of resistance to isoniazid. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. Risk of bias and applicability concerns were the same for Xpert MTB/XDR for detection of resistance to fluoroquinolone and amikacin.



In the patient selection domain, we considered four study cohorts (67%) to have low risk of bias (Penn-Nicholson 2021 India (Mumbai); Penn-Nicholson 2021 India (New Delhi); Penn-Nicholson 2021 Moldova; Penn-Nicholson 2021 South Africa), and two study cohorts to have unclear risk of bias because we could not tell if these study cohorts avoided inappropriate exclusions (Omar 2020 China; Omar 2020 South Africa). Regarding applicability for patient selection, we considered all study cohorts to have low concern.

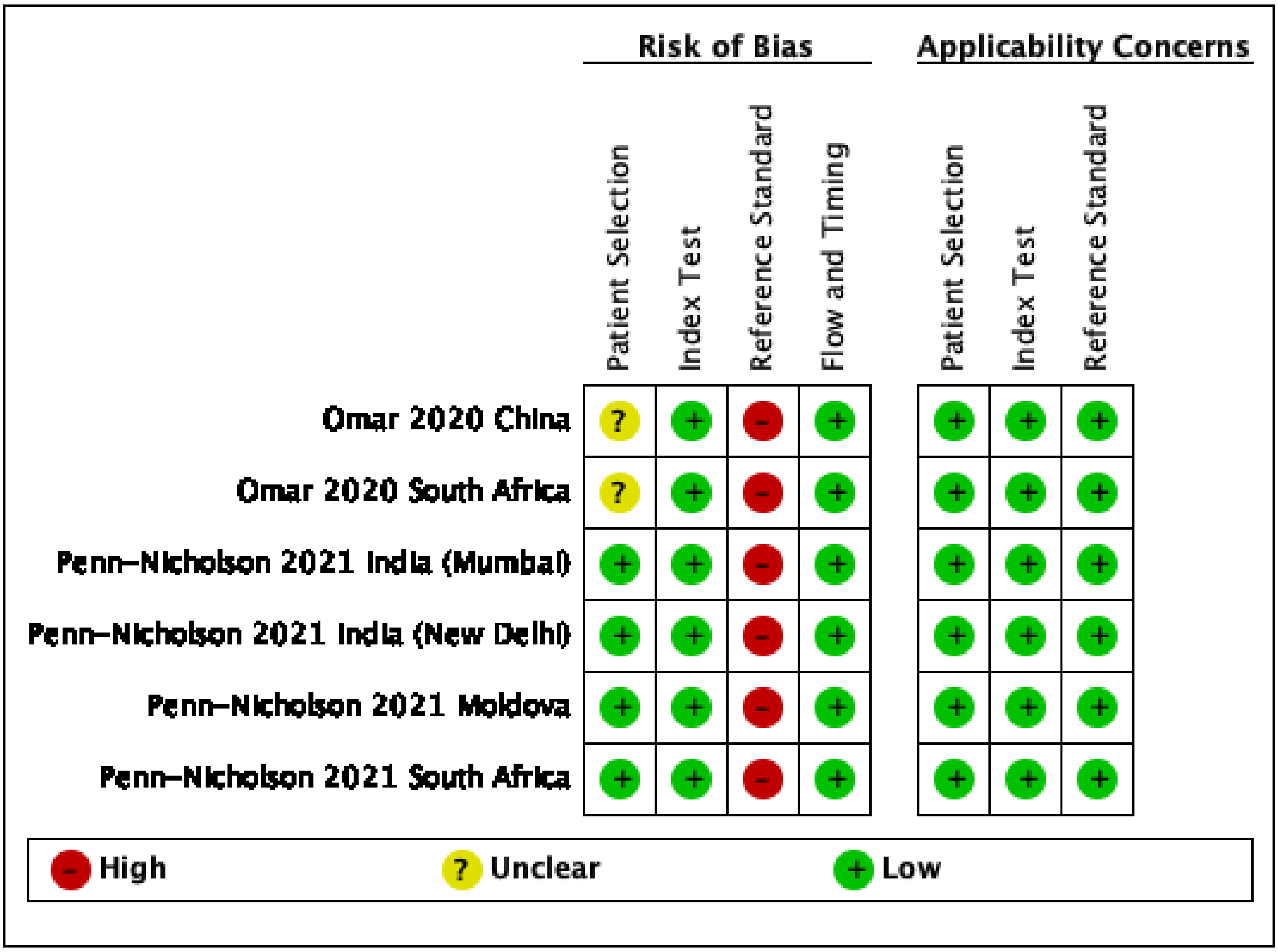
In the index test domain, we considered all study cohorts to have low risk of bias. Regarding applicability, for the index test domain, we considered all study cohorts to have low concern.

In the reference standard domain, for pDST and gDST, we considered all study cohorts have low risk of bias. Regarding applicability, for the reference standard domain, we considered all study cohorts to have low concern.

In the flow and timing domain, we considered all study cohorts to have low risk of bias.

Ethionamide resistance, Figure 6.

Figure 6. Xpert MTB/XDR for detection of resistance to ethionamide. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



For Xpert MTB/XDR for resistance to ethionamide, our assessment of methodological quality was the same as for resistance to the other drugs, except for risk of bias in the reference standard domain. For pDST and gDST, we judged all study cohorts to have high risk of bias. For pDST, this was owing to considerable overlap in the minimum inhibitory concentration (MIC)s of *M tuberculosis* isolates with and without resistance-causing variants. For gDST, this was because no study cohort included all loci required, *ethA*, *ethR*, and *inhA* promoter. We note that Omar 2020 China assessed Xpert MTB/XDR for ethionamide resistance only against the gDST reference standard, and not the pDST reference standard.

Conflicts of interest

One study reporting on two study cohorts was sponsored by the manufacturer (Omar 2020 China; Omar 2020 South Africa). We performed sensitivity analyses by repeating the meta-analyses and excluding these study cohorts (see Sensitivity analyses).

Findings

Detection of pulmonary tuberculosis

For Xpert MTB/XDR accuracy for detection of pulmonary tuberculosis, we identified two studies. One study reported data for two study cohorts (Omar 2020 China; Omar 2020 South Africa), and one study reported data for the study as a whole (Penn-Nicholson 2021), Figure 7. Xpert MTB/XDR sensitivity ranged from 98.3% (96.1 to 99.5) to 98.9% (96.2 to 99.9) and specificity from 22.5% (14.3 to 32.6) to 100.0% (86.3 to 100.0); the median prevalence of pulmonary tuberculosis was 91.3%, (interquartile range, 89.3% to 91.8%). In Penn-Nicholson 2021; the low specificity (22.5%) may in part be explained by inclusion of participants on tuberculosis treatment (40.1%). Such participants may have tested Xpert MTB/XDR positive and culture (reference standard) negative and been classified as false-positive. We did not perform a meta-analysis owing to heterogeneity in both the characteristics of participants and observed specificity estimates.

Figure 7. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for pulmonary tuberculosis against culture reference standard. TB: tuberculosis; TP = true positive; FP = false positive; FN = false negative; TN = true negative. For detection of pulmonary tuberculosis, only one study reported data for separate study cohorts. For smear-positive and smear-negative TB, data were not reported for separate study cohorts.

Xpert MTB/XDR, direct, TB detection, culture

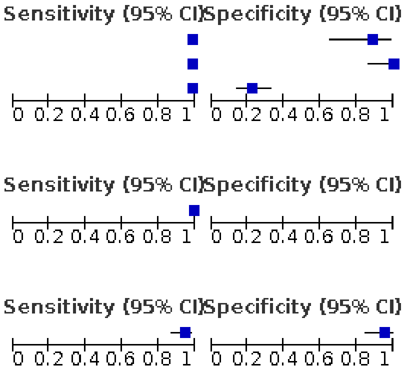
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	188	2	2	16	0.99 [0.96, 1.00]	0.89 [0.65, 0.99]
Omar 2020 South Africa	292	0	5	25	0.98 [0.96, 0.99]	1.00 [0.86, 1.00]
Penn-Nicholson 2021	599	69	10	20	0.98 [0.97, 0.99]	0.22 [0.14, 0.33]

Xpert MTB/XDR, direct, smear-positive TB, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020	398	0	2	0	0.99 [0.98, 1.00]	Not estimable

Xpert MTB/XDR, direct, smear-negative TB, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020	80	2	5	41	0.94 [0.87, 0.98]	0.95 [0.84, 0.99]



Detection of drug resistance

Forest plots for isoniazid resistance are presented in Figure 8, fluoroquinolone resistance in Figure 9, ethionamide resistance in Figure 10, and amikacin resistance in Figure 11. Xpert MTB/XDR summary sensitivity and specificity estimates for detection of drug resistance are presented in Table 2.

Figure 8. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for isoniazid resistance by population and reference standard. gDST = genotypic drug resistance testing; pDST = phenotypic drug resistance testing; TP = true positive; FP = false positive; FN = false negative; TN = true negative. Study in the forest plots refers to a study cohort within a multicentre study.

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	117	0	10	60	0.92 [0.86, 0.96]	1.00 [0.94, 1.00]
Omar 2020 South Africa	127	2	13	149	0.91 [0.85, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (Mumbai)	143	0	2	33	0.99 [0.95, 1.00]	1.00 [0.89, 1.00]
Penn-Nicholson 2021 India (New Delhi)	63	5	15	33	0.81 [0.70, 0.89]	0.87 [0.72, 0.96]
Penn-Nicholson 2021 Moldova	213	0	3	14	0.99 [0.96, 1.00]	1.00 [0.77, 1.00]
Penn-Nicholson 2021 South Africa	45	1	5	30	0.90 [0.78, 0.97]	0.97 [0.83, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	113	2	1	64	0.99 [0.95, 1.00]	0.97 [0.89, 1.00]
Omar 2020 South Africa	128	1	2	160	0.98 [0.95, 1.00]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	132	0	1	29	0.99 [0.96, 1.00]	1.00 [0.88, 1.00]
Penn-Nicholson 2021 India (New Delhi)	61	1	9	38	0.87 [0.77, 0.94]	0.97 [0.87, 1.00]
Penn-Nicholson 2021 Moldova	208	1	4	13	0.98 [0.95, 0.99]	0.93 [0.66, 1.00]
Penn-Nicholson 2021 South Africa	20	0	3	8	0.87 [0.66, 0.97]	1.00 [0.63, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	117	0	11	59	0.91 [0.85, 0.96]	1.00 [0.94, 1.00]
Omar 2020 South Africa	128	1	14	148	0.90 [0.84, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (Mumbai)	143	0	2	28	0.99 [0.95, 1.00]	1.00 [0.88, 1.00]
Penn-Nicholson 2021 India (New Delhi)	68	0	17	31	0.80 [0.70, 0.88]	1.00 [0.89, 1.00]
Penn-Nicholson 2021 Moldova	213	0	4	13	0.98 [0.95, 0.99]	1.00 [0.75, 1.00]
Penn-Nicholson 2021 South Africa	45	0	6	7	0.88 [0.76, 0.96]	1.00 [0.59, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	141	0	2	2	0.99 [0.95, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 India (New Delhi)	58	3	10	3	0.85 [0.75, 0.93]	0.50 [0.12, 0.88]
Penn-Nicholson 2021 Moldova	210	0	0	2	1.00 [0.98, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 South Africa	37	1	4	19	0.90 [0.77, 0.97]	0.95 [0.75, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	130	0	1	2	0.99 [0.96, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 India (New Delhi)	54	0	5	7	0.92 [0.81, 0.97]	1.00 [0.59, 1.00]
Penn-Nicholson 2021 Moldova	206	1	0	2	1.00 [0.98, 1.00]	0.67 [0.09, 0.99]
Penn-Nicholson 2021 South Africa	18	0	2	6	0.90 [0.68, 0.99]	1.00 [0.54, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	141	0	2	1	0.99 [0.95, 1.00]	1.00 [0.03, 1.00]
Penn-Nicholson 2021 India (New Delhi)	61	0	10	3	0.86 [0.76, 0.93]	1.00 [0.29, 1.00]
Penn-Nicholson 2021 Moldova	210	0	0	2	1.00 [0.98, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 South Africa	37	0	4	5	0.90 [0.77, 0.97]	1.00 [0.48, 1.00]

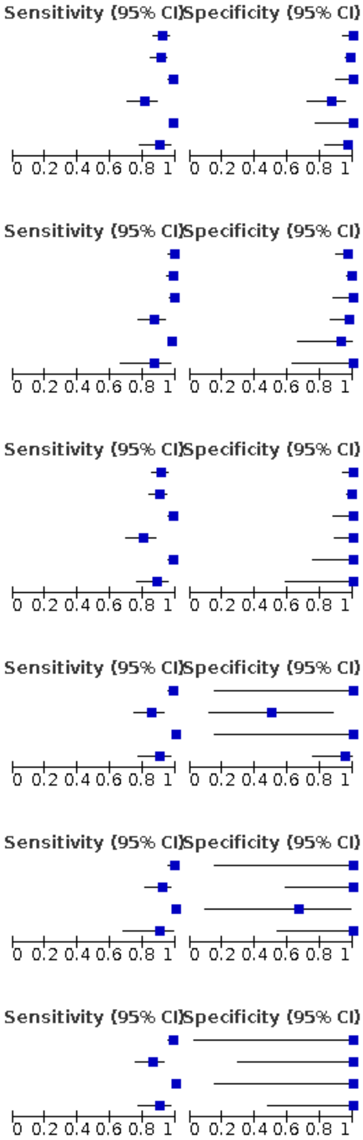
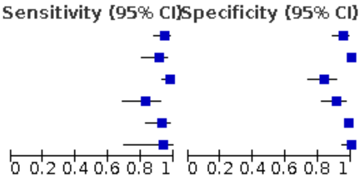


Figure 9. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for fluoroquinolone resistance by population and reference standard. Study in the forest plots refers to a study cohort within a multicentre study. gDST = genotypic drug resistance testing; pDST = phenotypic drug resistance testing; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

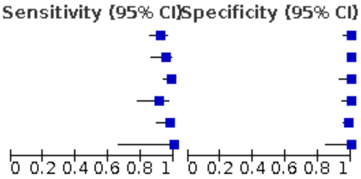
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	90	4	5	87	0.95 [0.88, 0.98]	0.96 [0.89, 0.99]
Omar 2020 South Africa	58	0	6	167	0.91 [0.81, 0.96]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	102	12	2	62	0.98 [0.93, 1.00]	0.84 [0.73, 0.91]
Penn-Nicholson 2021 India (New Delhi)	38	6	8	64	0.83 [0.69, 0.92]	0.91 [0.82, 0.97]
Penn-Nicholson 2021 Moldova	52	2	4	172	0.93 [0.83, 0.98]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	15	0	1	64	0.94 [0.70, 1.00]	1.00 [0.94, 1.00]



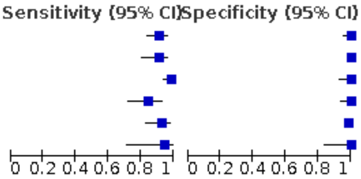
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	94	0	8	78	0.92 [0.85, 0.97]	1.00 [0.95, 1.00]
Omar 2020 South Africa	58	0	3	228	0.95 [0.86, 0.99]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	107	0	2	53	0.98 [0.94, 1.00]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 India (New Delhi)	39	0	4	66	0.91 [0.78, 0.97]	1.00 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	50	3	1	172	0.98 [0.90, 1.00]	0.98 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	9	0	0	22	1.00 [0.66, 1.00]	1.00 [0.85, 1.00]



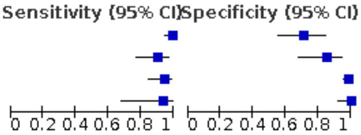
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	94	0	9	83	0.91 [0.84, 0.96]	1.00 [0.96, 1.00]
Omar 2020 South Africa	58	0	6	225	0.91 [0.81, 0.96]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	113	0	2	53	0.98 [0.94, 1.00]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 India (New Delhi)	44	0	8	61	0.85 [0.72, 0.93]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	52	2	4	169	0.93 [0.83, 0.98]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	16	0	1	21	0.94 [0.71, 1.00]	1.00 [0.84, 1.00]



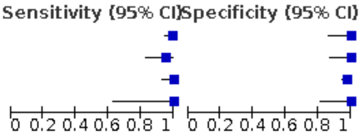
Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	102	12	1	30	0.99 [0.95, 1.00]	0.71 [0.55, 0.84]
Penn-Nicholson 2021 India (New Delhi)	37	5	4	28	0.90 [0.77, 0.97]	0.85 [0.68, 0.95]
Penn-Nicholson 2021 Moldova	51	2	3	156	0.94 [0.85, 0.99]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	14	0	1	45	0.93 [0.68, 1.00]	1.00 [0.92, 1.00]



Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	107	0	1	25	0.99 [0.95, 1.00]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 India (New Delhi)	37	0	2	27	0.95 [0.83, 0.99]	1.00 [0.87, 1.00]
Penn-Nicholson 2021 Moldova	50	3	0	156	1.00 [0.93, 1.00]	0.98 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	8	0	0	18	1.00 [0.63, 1.00]	1.00 [0.81, 1.00]



Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	113	0	1	25	0.99 [0.95, 1.00]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 India (New Delhi)	42	0	4	25	0.91 [0.79, 0.98]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 Moldova	51	2	3	153	0.94 [0.85, 0.99]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	15	0	1	17	0.94 [0.70, 1.00]	1.00 [0.80, 1.00]

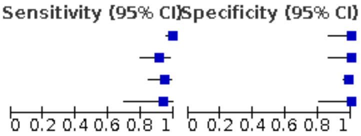
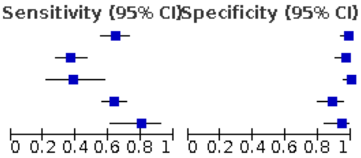


Figure 10. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for ethionamide resistance by population and reference standard. Study in the forest plots refers to a study cohort within a multicentre study. gDST = genotypic drug resistance testing; pDST = phenotypic drug resistance testing; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

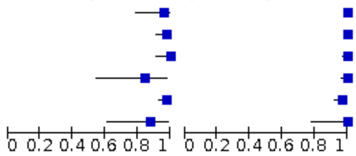
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	75	2	41	112	0.65 [0.55, 0.73]	0.98 [0.94, 1.00]
Penn-Nicholson 2021 India (Mumbai)	39	2	66	71	0.37 [0.28, 0.47]	0.97 [0.90, 1.00]
Penn-Nicholson 2021 India (New Delhi)	12	0	19	85	0.39 [0.22, 0.58]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	101	8	57	64	0.64 [0.56, 0.71]	0.89 [0.79, 0.95]
Penn-Nicholson 2021 South Africa	24	3	6	48	0.80 [0.61, 0.92]	0.94 [0.84, 0.99]



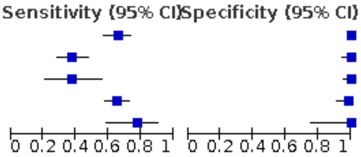
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	23	0	1	157	0.96 [0.79, 1.00]	1.00 [0.98, 1.00]
Omar 2020 South Africa	81	0	2	209	0.98 [0.92, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	39	0	0	123	1.00 [0.91, 1.00]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	11	0	2	96	0.85 [0.55, 0.98]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	103	4	2	117	0.98 [0.93, 1.00]	0.97 [0.92, 0.99]
Penn-Nicholson 2021 South Africa	14	0	2	15	0.88 [0.62, 0.98]	1.00 [0.78, 1.00]



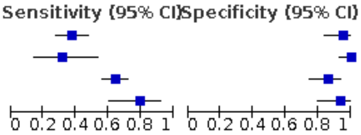
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	81	0	42	169	0.66 [0.57, 0.74]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	40	0	66	63	0.38 [0.29, 0.48]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	12	0	20	78	0.38 [0.21, 0.56]	1.00 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	108	1	57	62	0.65 [0.58, 0.73]	0.98 [0.91, 1.00]
Penn-Nicholson 2021 South Africa	24	0	7	13	0.77 [0.59, 0.90]	1.00 [0.75, 1.00]



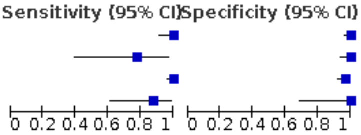
Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	39	2	65	39	0.38 [0.28, 0.48]	0.95 [0.83, 0.99]
Penn-Nicholson 2021 India (New Delhi)	8	0	17	49	0.32 [0.15, 0.54]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	100	8	55	49	0.65 [0.56, 0.72]	0.86 [0.74, 0.94]
Penn-Nicholson 2021 South Africa	23	2	6	30	0.79 [0.60, 0.92]	0.94 [0.79, 0.99]



Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	39	0	0	94	1.00 [0.91, 1.00]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	2	57	0.78 [0.40, 0.97]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	103	3	0	103	1.00 [0.96, 1.00]	0.97 [0.92, 0.99]
Penn-Nicholson 2021 South Africa	14	0	2	10	0.88 [0.62, 0.98]	1.00 [0.69, 1.00]



Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	40	0	65	35	0.38 [0.29, 0.48]	1.00 [0.90, 1.00]
Penn-Nicholson 2021 India (New Delhi)	8	0	18	42	0.31 [0.14, 0.52]	1.00 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	107	1	55	48	0.66 [0.58, 0.73]	0.98 [0.89, 1.00]
Penn-Nicholson 2021 South Africa	23	0	7	8	0.77 [0.58, 0.90]	1.00 [0.63, 1.00]

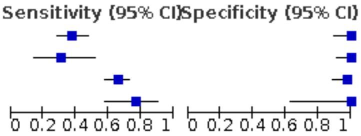


Figure 11. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for amikacin resistance by population and reference standard. Study in the forest plots refers to a study cohort within a multicentre study. gDST = genotypic drug resistance testing; pDST = phenotypic drug resistance testing; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	29	2	5	141	0.85 [0.69, 0.95]	0.99 [0.95, 1.00]
Omar 2020 South Africa	50	0	2	176	0.96 [0.87, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	153	0.83 [0.61, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	2	107	0.75 [0.35, 0.97]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 Moldova	10	8	2	210	0.83 [0.52, 0.98]	0.96 [0.93, 0.98]
Penn-Nicholson 2021 South Africa	21	0	1	59	0.95 [0.77, 1.00]	1.00 [0.94, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	31	0	2	144	0.94 [0.80, 0.99]	1.00 [0.97, 1.00]
Omar 2020 South Africa	50	0	1	235	0.98 [0.90, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	18	2	3	138	0.86 [0.64, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	12	92	0.29 [0.10, 0.56]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	203	0.77 [0.55, 0.92]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	19	1.00 [0.74, 1.00]	1.00 [0.82, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	31	0	5	147	0.86 [0.71, 0.95]	1.00 [0.98, 1.00]
Omar 2020 South Africa	50	0	2	234	0.96 [0.87, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	137	0.83 [0.61, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	14	89	0.30 [0.12, 0.54]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	203	0.77 [0.55, 0.92]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	18	0.95 [0.77, 1.00]	1.00 [0.81, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, pDST

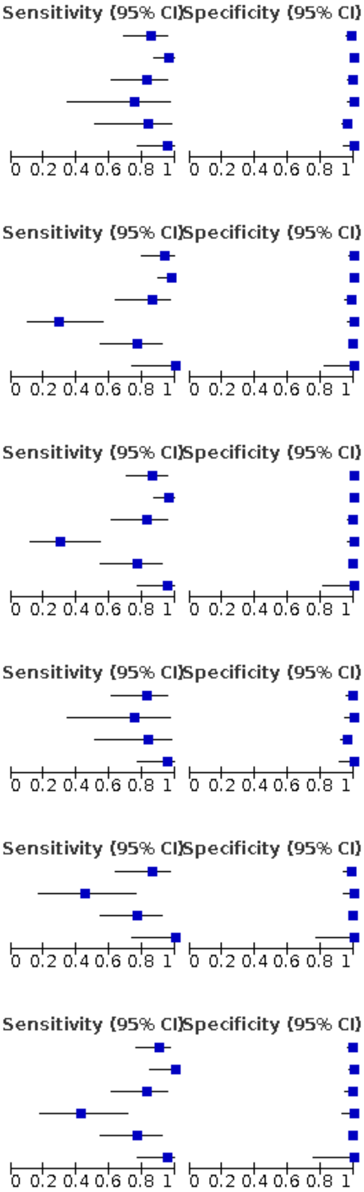
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	1	4	120	0.83 [0.61, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	2	65	0.75 [0.35, 0.97]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	10	8	2	192	0.83 [0.52, 0.98]	0.96 [0.92, 0.98]
Penn-Nicholson 2021 South Africa	21	0	1	39	0.95 [0.77, 1.00]	1.00 [0.91, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	18	2	3	109	0.86 [0.64, 0.97]	0.98 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	6	55	0.45 [0.17, 0.77]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	186	0.77 [0.55, 0.92]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	36	1	4	136	0.90 [0.76, 0.97]	0.99 [0.96, 1.00]
Omar 2020 South Africa	22	0	0	140	1.00 [0.85, 1.00]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	108	0.83 [0.61, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	8	53	0.43 [0.18, 0.71]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	186	0.77 [0.55, 0.92]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]



Xpert MTB/XDR by direct testing for resistance to isoniazid, fluoroquinolones, and amikacin

For detection of resistance to isoniazid and fluoroquinolones, Xpert MTB/XDR summary estimates for sensitivity and specificity were similar when different reference standards were used, both in people irrespective of rifampicin resistance and in people with rifampicin resistance. For detection of resistance to amikacin, Xpert MTB/XDR summary sensitivity estimates against gDST in the different populations were more variable.

We note that Xpert MTB/XDR sensitivity for detection of isoniazid resistance, Figure 8, and amikacin resistance, Figure 11 was lower in New Delhi than in other study cohorts.

Xpert MTB/XDR by direct testing for ethionamide resistance

For detection of ethionamide resistance, Xpert MTB/XDR summary estimates for sensitivity varied when different reference standards were used. Specificity values were more consistent in these analyses. We also note that against both pDST and a composite reference standard, Xpert MTB/XDR sensitivity for detection of ethionamide resistance was lower in New Delhi and Mumbai than in Moldova and South Africa, Figure 10.

Xpert MTB/XDR by direct testing for resistance to kanamycin and capreomycin

Forest plots of Xpert MTB/XDR sensitivity and specificity estimates for detection of kanamycin and capreomycin resistance are presented in Appendix 6.

For detection of kanamycin resistance, Xpert MTB/XDR summary sensitivity estimates were similar to those for amikacin. For detecting capreomycin resistance, Xpert MTB/XDR summary sensitivity estimates were lower than those for other drugs. Summary specificity estimates were more consistent in these analyses, Table 2.

Comparison Xpert MTB/XDR accuracy by direct testing versus indirect testing

One study compared Xpert MTB/XDR accuracy on sputum (direct testing) with cultured isolates (indirect testing) (Penn-Nicholson 2021). Data were not reported by study cohort. For each drug (isoniazid, fluoroquinolone, ethionamide, and amikacin), Xpert MTB/XDR accuracy for drug resistance by type of testing was similar, Appendix 7.

Inconclusive Xpert MTB/XDR results and missed cases

Data on inconclusive Xpert MTB/XDR results and missed cases are described in Appendix 5.

Non-determinate results

The summary proportion of Xpert MTB/XDR non-determinate results was estimated to be 2.90% (95% CI: 1.97% to 3.84%). The proportion of Xpert MTB/XDR non-determinate results following retesting was 0.2% (1/531) (Omar 2020) and 0.3% (2/709) (Penn-Nicholson 2021).

Xpert XDR/MTB indeterminate results

See Table 3.

One study provided information on retesting following an Xpert MTB/XDR indeterminate result (Penn-Nicholson 2021). No specimens were indeterminate upon retesting for resistance to isoniazid, fluoroquinolone, and ethionamide. Of 657 specimens tested by Xpert MTB/XDR for amikacin resistance, 23 (3.5%) had indeterminate results and 1/23 was indeterminate upon retesting.

Xpert MTB/XDR MTB NOT DETECTED

One study reported information about when Xpert MTB/XDR did not detect tuberculosis to begin with (missed cases) (Omar 2020). Results are summarized in Appendix 5.

Investigations of heterogeneity

Tuberculosis detection

Smear status

One study assessed Xpert MTB/XDR accuracy for pulmonary tuberculosis in smear-positive and smear-negative sputum specimens (Omar 2020), Figure 7. Data were not reported by study cohort. We note that Xpert MTB/XDR sensitivity in smear-negative specimens was higher than expected and may have been overestimated (see Discussion).

Drug resistance detection

Smear status

One study compared Xpert MTB/XDR sensitivity and specificity for drug resistance in smear-positive and smear-negative sputum specimens (Penn-Nicholson 2021). Data were not reported by study cohort. For a given drug (isoniazid, fluoroquinolone, ethionamide, and amikacin), Xpert MTB/XDR accuracy for detection of drug resistance was similar in smear-positive and smear-negative specimens, Appendix 8.

HIV status

One study compared Xpert MTB/XDR sensitivity and specificity for drug resistance in HIV-positive and HIV-negative people (Penn-Nicholson 2021). Data were not reported by study cohort. For resistance to isoniazid and fluoroquinolones, Xpert MTB/XDR sensitivity was similar, while for resistance to ethionamide and amikacin, Xpert MTB/XDR sensitivity was higher in HIV-positive people than in HIV-negative people, Appendix 9. There were few resistant samples in the HIV-positive subgroup compared to the HIV-negative subgroups, which could account for this variability. Xpert MTB/XDR specificity was high and consistent in all analyses.

Previous tuberculosis treatment

One study assessed Xpert MTB/XDR accuracy for detection of drug resistance in people with and without previous tuberculosis treatment (Penn-Nicholson 2021). Data were not reported by study cohort. There were no notable differences in Xpert MTB/XDR sensitivity or specificity for drug resistance in people who reported no previous tuberculosis treatment in the preceding 60 days versus those who reported receiving tuberculosis treatment in the preceding 60 days, Appendix 10.

Sensitivity analyses

Overall, the sensitivity analyses made little difference to the findings, Table 4.

DISCUSSION

This Cochrane Review summarizes the evidence on the diagnostic accuracy of Xpert MTB/XDR, a newly developed nucleic acid amplification test (NAAT) that detects pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin. We identified two multicentre studies reporting on a total of six independent study cohorts and including 1228 participants for pulmonary tuberculosis detection and 1141 participants for drug resistance detection. Both studies took place in high MDR/rifampicin-resistant tuberculosis burden countries. The review had notable limitations. For detection of pulmonary tuberculosis, in the patient selection domain, we judged all studies as having high risk of bias owing to selective participant recruitment. For detection of ethionamide resistance, in the reference standard domain, we judged high risk of bias for both phenotypic drug susceptibility testing (pDST) and genotypic drug susceptibility testing (gDST).

Summary of main results

- For detection of pulmonary tuberculosis, Xpert MTB/XDR sensitivity ranged from 98.3% (96.1 to 99.5) to 98.9% (96.2 to 99.9) and specificity from 22.5% (14.3 to 32.6) to 100.0% (86.3 to 100.0). The median prevalence of pulmonary tuberculosis in this analysis was 91.3%, (interquartile range, 89.3% to 91.8%).
- For resistance to isoniazid, in people irrespective of rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Xpert MTB/XDR summary sensitivity was 94.2% (87.5 to 97.4) against a reference standard of pDST.
- For resistance to fluoroquinolones, in people irrespective of rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Xpert MTB/XDR summary sensitivity was 93.2% (88.1 to 96.2) against a reference standard of pDST.
- For resistance to ethionamide, in people with known rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Xpert MTB/XDR summary sensitivity 98.0% (74.2 to 99.9) against a reference standard of gDST.
- For resistance to amikacin, in people with known rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Xpert MTB/XDR summary sensitivity was 86.1% (75.0 to 92.7) against a reference standard of pDST.
- Xpert MTB/XDR summary specificity for detection of any drug resistance was > 97.0% in most analyses.
- Overall, for resistance to isoniazid and fluoroquinolones, Xpert MTB/XDR sensitivity estimates for individual studies were consistent against the different reference standards.
- The summary proportion of Xpert MTB/XDR non-determinate results was estimated as 2.90% (95% CI: 1.97% to 3.84%).
- The summary proportion of Xpert MTB/XDR indeterminate results was estimated as 0.34% (0.00 to 0.68) for isoniazid resistance; 1.05% (0.46 to 1.64) for fluoroquinolone resistance; 0.06% (0.00 to 0.34) for ethionamide resistance; and 2.33% (1.46 to 3.20) for amikacin resistance.

For each drug, Xpert MTB/XDR summary sensitivity and specificity estimates were similar in people irrespective of rifampicin resistance and people with rifampicin resistance. However, we note that a high proportion of participants had known rifampicin resistance.

We were unable to perform most pre-specified analyses owing to sparse data.

Xpert MTB/XDR for pulmonary tuberculosis, Summary of findings 1.

In theory, of 1000 people with suspected pulmonary tuberculosis of whom 100 have tuberculosis: an estimated 98 to 99 people would have an Xpert MTB/XDR result indicating tuberculosis, of these 1 to 2 (1%) would be incorrectly classified as having tuberculosis (FP); and an estimated 203 to 900 people would have a result indicating the absence of tuberculosis, of these 0 to 697 (0% to 77%) would have tuberculosis (FN).

Xpert MTB/XDR for isoniazid resistance in people irrespective of rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Summary of findings 2.

In theory, of 1000 people with pulmonary tuberculosis detected as tuberculosis positive by Xpert MTB/XDR, where 50 have isoniazid resistance, 61 would have an Xpert MTB/XDR result indicating isoniazid resistance: of these, 14/61 (23%) would not have isoniazid resistance (FP); and 939 would have a result indicating the absence of isoniazid resistance: of these, 3/939 (0%) would have isoniazid resistance (FN).

Xpert MTB/XDR for fluoroquinolone resistance in people irrespective of rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Summary of findings 3

In theory, of 1000 people with pulmonary tuberculosis detected as tuberculosis positive by Xpert MTB/XDR, where 50 have fluoroquinolone resistance, 66 would have an Xpert MTB/XDR result indicating fluoroquinolone resistance: of these, 19/66 (29%) would not have fluoroquinolone resistance (FP) and 934 would have a result indicating the absence of fluoroquinolone resistance: of these, 3/934 (0%) would have fluoroquinolone resistance (FN).

Xpert MTB/XDR for ethionamide resistance in people with known rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Summary of findings 4.

In theory, of 1000 people with pulmonary tuberculosis detected as tuberculosis positive by Xpert MTB/XDR, where 300 have ethionamide resistance, 296 would have an Xpert MTB/XDR result indicating ethionamide resistance: of these, 2/296 (1%) would not have ethionamide resistance (FP) and 704 would have a result indicating the absence of ethionamide resistance: of these, 6/704 (1%) would have ethionamide resistance (FN).

Xpert MTB/XDR for amikacin resistance in people with known rifampicin resistance, detected as tuberculosis positive by Xpert MTB/XDR, Summary of findings 5.

In theory, of 1000 people with pulmonary tuberculosis detected as tuberculosis positive by Xpert MTB/XDR, where 135 have amikacin resistance, 126 would have an Xpert MTB/XDR result indicating amikacin resistance: of these, 10/126 (8%) would not have amikacin resistance (FP) and 874 would have a result indicating the absence of amikacin resistance: of these, 19/874 (2%) would have amikacin resistance (FN).

We noted that Xpert MTB/XDR sensitivity varied by study cohort. For detection of isoniazid and amikacin resistance, Xpert MTB/XDR sensitivity in New Delhi was considerably lower than in other study cohorts. For detection of ethionamide resistance, against both pDST and a composite reference standard, Xpert MTB/XDR sensitivity was lower in New Delhi and Mumbai than in Moldova and South Africa. Variants outside of those covered by the Xpert MTB/XDR assay may play a role in some settings, which could in part explain this variability.

For detection of capreomycin resistance, Xpert MTB/XDR summary sensitivity estimates were lower than those for resistance to other drugs. A Cochrane Review that assessed the diagnostic accuracy of MTBDR*sl* (a line probe assay) for resistance to second-line tuberculosis drugs showed a similar trend (Theron 2016b).

Xpert MTB/XDR is the first in a class of new technologies referred to as 'low complexity automated NAATs' for second-line drug-resistant tuberculosis. These new technologies are suitable for use in peripheral and intermediate level laboratories. Xpert MTB/XDR detects resistance to drugs other than rifampicin, namely isoniazid, fluoroquinolones, ethionamide, and amikacin (as well as kanamycin and capreomycin, second-line injectable drugs which are no longer recommended for people with MDR/rifampicin-resistant tuberculosis). However, WHO guidelines stress that the use of a low complexity automated NAAT to detect fluoroquinolone resistance does not eliminate the need for culture-based pDST, required to determine resistance to other tuberculosis drugs (e.g. bedaquiline, delamanid, other drugs) (WHO Consolidated Guidelines (Module 3) 2021).

Xpert MTB/XDR could guide treatment decisions and allow for rapid initiation of effective therapy, especially regarding the use of fluoroquinolones in people with drug-resistant tuberculosis. The use of Xpert MTB/XDR in people with rifampicin-susceptible tuberculosis could also improve the detection of isoniazid resistance. Furthermore, with the exciting advent of new rifapentine-based shortened regimens for drug-susceptible tuberculosis, with and without moxifloxacin (a fluoroquinolone), the potential impact of Xpert MTB/XDR has increased (Dorman 2021).

We found, based on our summary estimates, that Xpert MTB/XDR sensitivity and specificity met the minimal (lowest acceptable) criteria for WHO's target product profile (TPP) for drug susceptibility testing (DST) to be used at peripheral microscopy centres. However, there is considerable uncertainty in the estimates and the lower limits of the 95% CIs lie below the TPP targets (WHO TPP 2021):

- diagnostic sensitivity > 90% for detection of isoniazid and fluoroquinolone resistance and ≥ 80% sensitivity for detection of amikacin resistance when measured against the pDST reference standard;

- analytical specificity ≥ 98% for any tuberculosis drug for which the test is able to identify resistance when compared with gDST as the reference standard.

Nonetheless, several challenges and questions need to be considered.

Xpert MTB/XDR must first detect tuberculosis, even if an individual is already tuberculosis-positive by another test, before it can generate a resistant or susceptible result. Our ability to assess Xpert MTB/XDR accuracy for detection of pulmonary tuberculosis was limited by the available data, which we considered to be at high risk of bias due to selective participant recruitment. As Xpert MTB/XDR is likely to be used as a follow-on test to an initial test that detects tuberculosis and rifampicin resistance (i.e. Xpert MTB/RIF, Xpert MTB/RIF Ultra, Truenat MTB, and Truenat MTB Plus), this approach would miss isoniazid or fluoroquinolone mono-resistant tuberculosis. Furthermore, if a patient has an Xpert MTB/RIF Ultra-trace positive result, they are unlikely to be detected as tuberculosis-positive by Xpert MTB/XDR. Xpert MTB/XDR, unlike Xpert MTB/RIF Ultra, relies on detection of a single rather than multicopy gene and Xpert MTB/RIF Ultra trace results occur only when the multicopy target is detected (Cepheid package insert 2021). As mentioned previously, the limit of detection of Xpert MTB/XDR for *M tuberculosis* is 71.9 colony-forming units (CFU)/mL, not as low as the limit of detection of Xpert MTB/RIF Ultra (15.6 CFU/mL) (Cao 2021; Chakravorty 2017).

Additionally, even if patients are Xpert MTB/RIF Ultra-positive, it is possible that the numbers and ability of bacteria to grow would decrease due to empiric treatment prior to a specimen being sent for Xpert MTB/XDR testing. This could result in a loss of culture-positivity (and preclude downstream pDST testing) even if Xpert MTB/XDR remains positive for tuberculosis due to the presence of MTB DNA. When tuberculosis is detected, the test may still report an indeterminate result for detection of drug resistance, though we found the summary proportion of indeterminate results to be low (≤ 2%). If Xpert MTB/XDR is done on sample reagent-treated sputum initially used for tuberculosis detection using Xpert MTB/RIF Ultra, the sample reagent may have, depending on storage conditions and duration, detrimentally affected DNA in the sputum in a manner that detracts from Xpert MTB/XDR performance (Banada 2010). This is an implementation challenge that requires further study.

The WHO positions Xpert MTB/XDR as a follow-on test for detection of additional drug resistance. However, the WHO has also set as a research priority the evaluation of Xpert MTB/XDR as an initial test for tuberculosis detection in people with signs and symptoms of tuberculosis (WHO Consolidated Guidelines (Module 3) 2021).

Non-actionable results (results which do not allow for clinician decisions) include all kinds of results (Xpert MTB/XDR MTB NOT DETECTED, non-determinate, indeterminate). This issue, which is a problem with MTBDR*sl* (a line probe assay), is becoming increasingly important as we seek to expand rapid DST (direct testing), including to those who are paucibacillary (tuberculosis disease caused by a small number of bacteria) and smear-negative and in whom tuberculosis detection by reflex DST would therefore be challenging. Our review had limited data to assess the number of people with tuberculosis who were missed (not detected as tuberculosis-positive by Xpert MTB/XDR to begin with), and would have drug susceptibility results uncharacterised by Xpert MTB/XDR.

In our review, in people with smear-negative specimens, Xpert MTB/XDR sensitivity (95% CI) for detection of pulmonary tuberculosis was 94% (87% to 98%) (based on one study) and may have been overestimated. We considered this study to have high risk of bias for participant selection. In contrast, a recent Cochrane Review found, in smear-negative (culture-positive) specimens, summary sensitivity of 77.5% (67.6 to 85.6) for Xpert MTB/RIF Ultra and 60.6% (48.4 to 71.7) for Xpert MTB/RIF (7 studies) (Zifodya 2021).

We did not have sufficient data to assess Xpert MTB/XDR accuracy for detection of pulmonary tuberculosis in people with and without previous tuberculosis treatment. This is an important concern as the test may report results for drug resistance in people who are detected as MTB-positive, but are in fact culture-negative. The related tests, Xpert MTB/RIF (Theron 2016a) and Xpert MTB/RIF Ultra (Mishra 2020), have diminished specificity in people with previous tuberculosis treatment. Importantly, since people with a history of tuberculosis have a higher risk of drug resistance compared to people who have not had tuberculosis before (WHO Global Tuberculosis Report 2021), DST is more likely to be done in this group.

Regarding detection of ethionamide resistance, Xpert MTB/XDR accuracy is based only on the detection of mutations in the *inhA* promoter region. Hence this limits the test's value in decision making for ruling-out resistance.

Heteroresistance, the clinical significance of which is uncertain, can be challenging for molecular tests to detect (pDST is generally the best method for detecting minority populations) and may in part explain Xpert MTB/XDR false-negative results. However, more data are needed on the ability of Xpert MTB/XDR to detect heteroresistance.

Finally, we wish to underscore that an all-in-one test for tuberculosis drug resistance would be highly desirable. However, detecting resistance to additional drugs using Xpert MTB/XDR may not be technologically feasible without great expense or loss of other gene targets.

Strengths and weaknesses of the review

Strengths and weaknesses of the review process

We were unable to perform several analyses as originally intended in the protocol because the paucity of data precluded pre-specified investigations of heterogeneity. When we observed heterogeneity and could not explore potential sources of heterogeneity, we took this into account when deciding whether to downgrade for inconsistency.

Strengths and weaknesses due to methodological quality assessment

For tuberculosis detection, as assessed by QUADAS-2, in the patient selection domain, we considered all study cohorts (100%) to have high risk of bias. The high proportion (> 90%) of participants with tuberculosis suggests that there was selective recruitment. For drug resistance detection, in the reference standard domain, both studies had low risk of bias for resistance to isoniazid, fluoroquinolones, and amikacin, and high risk of bias for resistance to ethionamide (for both pDST and gDST). Both studies used the critical concentrations for pDST currently recommended by the WHO.

Completeness of evidence

The findings in this review were based on comprehensive searching, strict selection criteria, and standardized data extraction. To identify studies, we searched multiple databases up to 23 September 2021 without language restriction. However, we acknowledge that we may have missed studies despite the comprehensive search. We corresponded with primary study authors to obtain additional data and information that was missing from the papers. The small number of studies and small number of participants in several of the analyses affected the precision of the results.

Accuracy of the reference standards used

Detection of pulmonary tuberculosis

Culture is regarded as the best available reference standard for the bacteriological confirmation of pulmonary tuberculosis and was the reference standard for detection of pulmonary tuberculosis in this review. Liquid culture is considered to be more sensitive than solid culture (Lewinsohn 2017). Liquid culture or both solid and liquid culture were the reference standards in these analyses.

Detection of drug resistance

As recommended by the WHO, we used culture-based pDST as the main reference standard for isoniazid resistance, fluoroquinolone resistance, and amikacin resistance (WHO TPP 2021). Culture involves growing an inoculum (the introduction of the bacteria into a culture medium) in the absence of a drug. This could lead to resistant bacteria present in the original specimen diminishing below the limit of detection of the reference standard method due to competition with the other drug-susceptible bacteria in the inoculum.

We used gDST as the main reference standard for ethionamide resistance because there is considerable overlap in the minimum inhibitory concentrations of *M tuberculosis* isolates with and without resistance-causing variants and a pDST reference standard might not correctly classify the target condition. Ethionamide resistance caused by *inhA* mutations is detected by the Xpert MTB/XDR, however, the test may not detect all variants of ethionamide resistance. We note that the gDST reference standard used only included the *inhA* promoter.

Applicability of findings to the review question

For detection of pulmonary tuberculosis, owing to inclusion of participants based on Xpert MTB/RIF- and Xpert MTB/RIF Ultra-positive results, we had high concern about applicability of the findings to the review question. For detection of drug resistance, the two multicentre studies (reporting on six study cohorts) took place at sites located in high MDR/rifampicin-resistant tuberculosis burden countries. However, two study cohorts were in India and two were in South Africa, possibly limiting applicability to other settings.

AUTHORS' CONCLUSIONS

Implications for practice

The review findings suggest that Xpert MTB/XDR provides accurate results for detection of isoniazid and fluoroquinolone resistance and can assist with selection of an optimal treatment regimen. Given that Xpert MTB/XDR targets a limited number of resistance variants in specific genes, the test may perform differently in different settings. Findings in this review should, therefore, be interpreted with caution. Xpert MTB/XDR sensitivity for ethionamide resistance detection was based only on detection of mutations in the *inhA* promoter region by Xpert MTB/XDR, a known limitation. High risk of bias limits our confidence in Xpert MTB/XDR accuracy for pulmonary tuberculosis.

The impact of Xpert MTB/XDR is expected to be affected by the test's ability to detect tuberculosis (required for drug susceptibility testing (DST)), prevalence of resistance to a given drug, health care infrastructure, and access to other tests.

Implications for research

Future studies should assess the accuracy of Xpert MTB/XDR in different population groups, including children and people living with HIV. In addition, studies should assess the accuracy of Xpert MTB/XDR in different geographical settings, in smear-negative specimens, and with different types of clinical specimens. Assessing Xpert MTB/XDR accuracy in people who have previously received tuberculosis treatment is an important research gap and will inform whether confirmatory indirect testing of cultured isolates is feasible. Studies should also evaluate Xpert MTB/XDR as an initial test for tuberculosis detection, in addition to use as a follow-on test in all people with signs and symptoms of tuberculosis. Studies should assess the proportion of people with tuberculosis who are missed (not detected as tuberculosis-positive by Xpert MTB/XDR to begin with), and would have drug susceptibility results uncharacterised by Xpert MTB/XDR. Studies are needed to understand whether new tuberculosis diagnostics, such as Xpert MTB/XDR, influence mortality and other health outcomes important to people. Such studies may inform the use of this test on both diagnostic and treatment pathways.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Omar 2020

Study characteristics	
Patient Sampling	Cross-sectional, the manner of participant selection was not random or consecutive For drug resistance detection, MTB positive specimens were characterized by pDST and gDST prior to or during the study
Patient characteristics and setting	Presenting signs and symptoms: not reported; archived frozen raw sputum or sputum sediment specimens Exclusions: specimens that had been previously thawed were excluded; < 1 mL of frozen sputum sediment or < 2 mL of raw sputum Prior testing: archived (frozen) specimens confirmed to be MTB positive or negative by culture; Xpert MTB/RIF or Xpert MTB/RIF Ultra Age: ≥ 15 years (range, 13 to > 80 years; one participant was 13 years) in full study Sex, female: 38% HIV infection: China (0%); South Africa not reported Previous TB treatment: not reported Treatment of current episode: 199 (37.5%) study participated were reported to be on treatment, 6 (1.1%) were reported to not be on treatment and treatment status was unknown/not available for 325 study participants Sample size: 530; 254 (47.9%) with known rifampicin resistance Clinical setting: outpatient and inpatient Laboratory level: central Country: China, South Africa World Bank Income Classification: China (middle income) and South Africa (middle income) High TB burden country: China (yes), South Africa (yes) High TB/HIV burden country: China (yes), South Africa (yes) High MDR-TB burden country: China (yes), South Africa (yes)
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Culture with MGIT or LJ culture; Xpert MTB/RIF and Xpert MTB/RIF Ultra Resistance to: isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, capreomycin pDST, gDST, composite reference standard China: INH High 0.4 mg/L; INH Low 0.1 mg/L; MFX High 2.0 and Low 0.5 mg/L; OFX: 2.0 mg/L; ETO not done; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP not done South Africa: INH High 0.4 mg/L Low 0.1 mg/L; MFX High 1.0 and Low 0.25 mg/L; OFX 2.0 mg/L; LVX 1.0 mg/L; ETO 5.0 mg/L; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L There were 8 gene targets of interest (*katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, gyrA, gyrB, rrs*, *eis* promoter) were reported

Omar 2020 *(Continued)*

Flow and timing	3 patients were excluded due to insufficient volume and 1 patient for non-determinate Xpert MTB/XDR result. For ethionamide, pDST results were not available for 270/530 (50.9%) of participants.
Comparative	
Notes	The composite reference result was considered drug resistant if the pDST was reported as drug resistant or the sequencing results had detected a drug associated resistant mutation. The composite reference result was considered drug susceptible when both pDST reported drug susceptibility and sequencing did not detect a drug associated resistant mutation. Analyses were undertaken where sequencing data associated with the specimen were reviewed to identify the location and type of mutations present for the drug resistance targets or if the specimen was wild type. The intent of the eligibility criteria was that all specimens used for testing would be characterized and have data available prior to enrolment; however, this was not possible as many specimens available at the study sites had MTB culture results, but did not have other data required. Study sites attempted to complete any missing pDST, sequencing, and Xpert MTB/RIF or Xpert MTB/RIF Ultra testing in parallel with Xpert MTB/XDR testing during the study. Sequencing method: China - Sanger Sequencing: targeted genes in supernatant DNA were amplified by designated primers and sent for Sanger sequencing; South Africa – Whole Genome Sequencing using NGS on the Illumina MiSeq using paired end sequencing methodology (2 x 300bp).

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Omar 2020 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Omar 2020 China

Study characteristics	
Patient Sampling	Cross-sectional, the manner of participant selection was not random or consecutive For drug resistance detection, MTB positive specimens were characterized by pDST and gDST prior to or during the study

Omar 2020 China *(Continued)*

Patient characteristics and setting	Presenting signs and symptoms: not reported; archived frozen raw sputum or sputum sediment specimens Exclusions: specimens that had been previously thawed were excluded; < 1 mL of frozen sputum sediment or < 2 mL of raw sputum Prior testing: archived (frozen) specimens confirmed to be MTB positive or negative by culture; Xpert MTB/RIF or Xpert MTB/RIF Ultra Age: ≥ 15 years (range, 13 to > 80 years; one participant was 13 years) in full study Sex, female: 38% in full study HIV infection: 0% Previous TB treatment: not reported Treatment of current episode: 199 (37.5%) study participated were reported to be on treatment, 6 (1.1%) were reported to not be on treatment and treatment status was unknown/not available for 325 study participants (parent study) Sample size: 208 Clinical setting: outpatient and inpatient Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Culture with MGIT or LJ culture; Xpert MTB/RIF and Xpert MTB/RIF Ultra Resistance to: isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, capreomycin (not done) pDST, gDST, composite reference standard INH High 0.4 mg/L; INH Low 0.1 mg/L; MFX High 2.0 and Low 0.5 mg/L; OFX: 2.0 mg/L; ETO not done; AMK 1.0 mg/L; KAN 2.5 mg/L There were 8 gene targets of interest (*katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, gyrA, gyrB, rrs*, *eis* promoter) were reported
Flow and timing	
Comparative	
Notes	The composite reference result was considered drug resistant if the pDST was reported as drug resistant or the sequencing results had detected a drug associated resistant mutation. The composite reference result was considered drug susceptible when both pDST reported drug susceptibility and sequencing did not detect a drug associated resistant mutation.

Omar 2020 China *(Continued)*

Discrepant analysis was undertaken where sequencing data associated with the specimen were reviewed to identify the location and type of mutations present for the drug resistance targets or if the specimen was wild type.
The intent of the eligibility criteria was that all specimens used for testing would be characterized and have data available prior to enrolment; however, this was not possible as many specimens available at the study sites had MTB culture results, but did not have other data required. Study sites attempted to complete any missing pDST, sequencing, and Xpert MTB/RIF or Xpert MTB/RIF Ultra testing in parallel with Xpert MTB/XDR testing during the study

Sequencing method: Sanger Sequencing: targeted genes in supernatant DNA were amplified by designated primers and sent for Sanger sequencing

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Omar 2020 China *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Omar 2020 South Africa

Study characteristics	
Patient Sampling	Cross-sectional, the manner of participant selection was not random or consecutive For drug resistance detection, MTB positive specimens were characterized by pDST and gDST prior to or during the study
Patient characteristics and setting	Presenting signs and symptoms: not reported; archived frozen raw sputum or sputum sediment specimens Exclusions: specimens that had been previously thawed were excluded; < 1 mL of frozen sputum sediment or < 2 mL of raw sputum Prior testing: archived (frozen) specimens confirmed to be MTB positive or negative by culture; Xpert MTB/RIF or Xpert MTB/RIF Ultra Age: ≥ 15 years (range, 13 to > 80 years; one participant was 13 years) in full study Sex, female: 38% in full study HIV infection: not reported Previous TB treatment: not reported Treatment of current episode: 199 (37.5%) study participated were reported to be on treatment, 6 (1.1%) were reported to not be on treatment and treatment status was unknown/not available for 325 study participants (parent study)

Omar 2020 South Africa *(Continued)*

	Sample size: 322 Clinical setting: outpatient and inpatient Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Culture with MGIT or LJ culture; Xpert MTB/RIF and Xpert MTB/RIF Ultra Resistance to: isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, capreomycin pDST, gDST, composite reference standard INH High 0.4 mg/L Low 0.1 mg/L; MFX High 1.0 and Low 0.25 mg/L; OFX 2.0 mg/L; LVX 1.0 mg/L; ETO 5.0 mg/L; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L There were 8 gene targets of interest (*katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, gyrA, gyrB, rrs*, *eis* promoter)
Flow and timing	
Comparative	
Notes	The composite reference result was considered drug resistant if the pDST was reported as drug resistant or the sequencing results had detected a drug associated resistant mutation. The composite reference result was considered drug susceptible when both pDST reported drug susceptibility and sequencing did not detect a drug associated resistant mutation. Discrepant analysis was undertaken where sequencing data associated with the specimen were reviewed to identify the location and type of mutations present for the drug resistance targets or if the specimen was wild type. The intent of the eligibility criteria was that all specimens used for testing would be characterized and have data available prior to enrolment; however, this was not possible as many specimens available at the study sites had MTB culture results, but did not have other data required. Study sites attempted to complete any missing pDST, sequencing, and Xpert MTB/RIF or Xpert MTB/RIF Ultra testing in parallel with Xpert MTB/XDR testing during the study. Sequencing method: South Africa – Whole Genome Sequencing using NGS on the Illumina MiSeq using paired end sequencing methodology (2 x 300bp)

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Omar 2020 South Africa *(Continued)*

Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Omar 2020 South Africa *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Penn-Nicholson 2021

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective Participants were prescreened for pulmonary tuberculosis symptoms and the presence of at least one risk factor for drug-resistant tuberculosis. Participants who met screening criteria received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those found to be Xpert MTB/RIF MTBC-positive or Xpert MTB/RIF Ultra MTBC-positive were enrolled. More than half of the population was also preselected for rifampicin resistance (and not just pulmonary tuberculosis). Screening was random and enrolment was consecutive and sequential for the two phases
Patient characteristics and setting	Presenting signs and symptoms: symptoms suggestive of pulmonary tuberculosis, i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis), and at least one of the following. - Previously received > 1 month of treatment for a prior tuberculosis episode or - Failing TB treatment with positive sputum smear or culture after ≥ 3 months of a standard TB treatment or - Had close contact with a known drug-resistant TB case or - Newly diagnosed with MDR-TB within the last 30 days or - Previously diagnosed with MDR-TB and failed TB treatment with positive sputum smear or culture after ≥ 3 months of a standard MDR-TB treatment regimen Exclusions for enrolment: sputum volume < 3 mL Age: ≥ 18 years; median 37 years (range 18 to 77) Sex, female: 214/611 (35%) HIV infection: 69/425 (16%) Previous TB treatment: 286 participants had received > 1 month of treatment for a previous tuberculosis episode Sample size: 698 for tuberculosis detection; 611 for resistance detection; 494/611 (80.9%) with known rifampicin resistance Clinical setting: outpatient and inpatient Laboratory level: central Country: India (Mumbai), India (New Delhi), Moldova, South Africa World Bank Income Classification: Moldova (middle income), India (middle income), South Africa (middle income)

Penn-Nicholson 2021 *(Continued)*

	High TB burden country: Moldova (no), India (yes), South Africa (yes) High TB/HIV burden country: Moldova (no), India (yes), South Africa (yes) High MDR-TB burden country: Moldova (yes), India (yes), South Africa (yes)
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert MTB/RIF and Xpert MTB/RIF Ultra Resistance to isoniazid, fluoroquinolones, moxifloxacin, levofloxacin, ethionamide, amikacin, kanamycin, capreomycin INH 0.1 mg/L; MFX High 1.0 mg/L and Low 0.25 mg/L; LFX 1.0 mg/L; ETO 5.0 mg/; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L pDST (MGIT960), gDST (whole genome sequencing), composite Genetic loci required for resistance testing criteria satisfied for isoniazid, fluoroquinolones, and amikacin gene targets: *katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, rpoB, gyrA, gyrB, rrs, eis* promoter
Flow and timing	
Comparative	
Notes	99/710 participants (13.9%) were excluded and accounted for owing to the following. • Culture negative: 89/99 (89.9%) • Culture positive but MTBC not identified: 3 • Culture contaminated: 5 • Culture result missing (but Xpert XDR available): 1 • No valid Xpert XDR results: 1 There was 1 indeterminate result for amikacin resistance in a specimen that was amikacin resistant by pDST. This specimen was gDST susceptible.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	

Penn-Nicholson 2021 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Penn-Nicholson 2021 India (Mumbai)

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective Participants were prescreened for pulmonary tuberculosis symptoms and the presence of at least one risk factor for drug-resistant tuberculosis. Participants who met screening criteria received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those found to be Xpert MTB/RIF MTBC-positive or Xpert MTB/RIF Ultra MTBC-positive were enrolled. More than half of the population was also preselected for rifampicin resistance (and not just pulmonary tuberculosis). Screening was random and enrolment was consecutive and sequential for the two phases
Patient characteristics and setting	Presenting signs and symptoms: symptoms suggestive of pulmonary tuberculosis, i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis), and at least one of the following. - Previously received > 1 month of treatment for a prior tuberculosis episode or - Failing TB treatment with positive sputum smear or culture after ≥ 3 months of a standard TB treatment or - Had close contact with a known drug-resistant TB case or - Newly diagnosed with MDR-TB within the last 30 days or - Previously diagnosed with MDR-TB and failed TB treatment with positive sputum smear or culture after ≥ 3 months of a standard MDR-TB treatment regimen Exclusions for enrolment: sputum volume < 3 mL Age: ≥ 18 years; median 31 years (range 18 to 77) Sex, female: 88/179 (49%) HIV infection: 1/42 (2%) Previous TB treatment: 286 participants had received >1 month of treatment for a previous tuberculosis episode (in the full study) Sample size: 179; 146/179 (82%) with known rifampicin resistance Clinical setting: outpatient and inpatient in the full study Laboratory level: central Country: India (Mumbai) World Bank Income Classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert MTB/RIF and Xpert Ultra

Penn-Nicholson 2021 India (Mumbai) *(Continued)*

	Resistance to isoniazid, fluoroquinolones, moxifloxacin, levofloxacin, ethionamide, amikacin, kanamycin, capreomycin INH 0.1 mg/L; MFX High 1.0 mg/L and Low 0.25 mg/L; LFX 1.0 mg/; ETO 5.0 mg/; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L pDST (MGIT960), gDST (whole genome sequencing), composite Genetic loci required for resistance testing criteria satisfied for isoniazid, fluoroquinolones, and amikacin gene targets: *katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, rpoB, gyrA, gyrB, rrs, eis* promoter
Flow and timing	
Comparative	
Notes	The study was designed to assess the diagnostic accuracy of Xpert MTB/XDR as a reflex test to detect tuberculosis drug resistance, and not detection of pulmonary tuberculosis. The study population was previously positive for tuberculosis by Xpert MTB/RIF or Xpert MTB/RIF Ultra testing

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Penn-Nicholson 2021 India (Mumbai) *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Penn-Nicholson 2021 India (New Delhi)

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective Participants were prescreened for pulmonary tuberculosis symptoms and the presence of at least one risk factor for drug-resistant tuberculosis. Participants who met screening criteria received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those found to be Xpert MTB/RIF MTBC-positive or Xpert MTB/RIF Ultra MTBC-positive were enrolled. More than half of the population was also preselected for rifampicin resistance (and not just pulmonary tuberculosis). Screening was random and enrolment was consecutive and sequential for the two phases
Patient characteristics and setting	Presenting signs and symptoms: symptoms suggestive of pulmonary tuberculosis, i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis), and at least one of the following. - Previously received > 1 month of treatment for a prior tuberculosis episode or

Penn-Nicholson 2021 India (New Delhi) *(Continued)*

	- Failing TB treatment with positive sputum smear or culture after ≥ 3 months of a standard TB treatment or - Had close contact with a known drug-resistant TB case or - Newly diagnosed with MDR-TB within the last 30 days or - Previously diagnosed with MDR-TB and failed TB treatment with positive sputum smear or culture after ≥ 3 months of a standard MDR-TB treatment regimen Exclusions for enrolment: sputum volume < 3 mL Age: ≥ 18 years; median 30 years (range 18 to 72) Sex, female: 52/120 (43%) HIV infection: 0% Previous TB treatment: 286 participants had received >1 month of treatment for a previous tuberculosis episode (in the full study) Sample size: 120; 75/120 (63%) with known rifampicin resistance Clinical setting: outpatient and inpatient in the full study Laboratory level: central Country: India (Delhi) World Bank Income Classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert MTB/RIF and Xpert Ultra Resistance to isoniazid, fluoroquinolones, moxifloxacin, levofloxacin, ethionamide, amikacin, kanamycin, capreomycin INH 0.1 mg/L; MFX High 1.0 mg/L and Low 0.25 mg/L; LFX 1.0 mg/L; ETO 5.0 mg/L; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L pDST (MGIT960), gDST (whole genome sequencing), composite Genetic loci required for resistance testing criteria satisfied for isoniazid, fluoroquinolones, and amikacin gene targets: *katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, rpoB, gyrA, gyrB, rrs, eis* promoter
Flow and timing	
Comparative	
Notes	The study was designed to assess the diagnostic accuracy of Xpert MTB/XDR as a reflex test to detect tuberculosis drug resistance, and not detection of pulmonary tuberculosis. The

Penn-Nicholson 2021 India (New Delhi) *(Continued)*

	study population was previously positive for tuberculosis by Xpert MTB/RIF or Xpert MTB/RIF Ultra testing

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

Penn-Nicholson 2021 India (New Delhi) *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Penn-Nicholson 2021 Moldova

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective Participants were prescreened for pulmonary tuberculosis symptoms and the presence of at least one risk factor for drug-resistant tuberculosis. Participants who met screening criteria received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those found to be Xpert MTB/RIF MTBC-positive or Xpert MTB/RIF Ultra MTBC-positive were enrolled. More than half of the population was also preselected for rifampicin resistance (and not just pulmonary tuberculosis). Screening was random and enrolment was consecutive and sequential for the two phases
Patient characteristics and setting	Presenting signs and symptoms: symptoms suggestive of pulmonary tuberculosis, i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis), and at least one of the following. - Previously received > 1 month of treatment for a prior tuberculosis episode or - Failing TB treatment with positive sputum smear or culture after ≥ 3 months of a standard TB treatment or - Had close contact with a known drug-resistant TB case or - Newly diagnosed with MDR-TB within the last 30 days or - Previously diagnosed with MDR-TB and failed TB treatment with positive sputum smear or culture after ≥ 3 months of a standard MDR-TB treatment regimen Exclusions for enrolment: sputum volume < 3 mL Age: ≥ 18 years; median 43 years (range 18 to 70) Sex, female: 45/230 (20%) HIV infection: 27/230 (12%) Previous TB treatment: 286 participants had received >1 month of treatment for a previous tuberculosis episode (in the full study) Sample size: 230; 212/230 (92%) with known rifampicin resistance Clinical setting: outpatient and inpatient in full study

Penn-Nicholson 2021 Moldova *(Continued)*

	Laboratory level: central Country: Republic of Moldova World Bank Income Classification: middle income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: yes		
Index tests	Xpert MTB/XDR		
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert MTB/RIF and Xpert Ultra Resistance to isoniazid, fluoroquinolones, moxifloxacin, levofloxacin, ethionamide, amikacin, kanamycin, capreomycin INH 0.1 mg/L; MFX High 1.0 mg/L and Low 0.25 mg/L; LFX 1.0 mg/L; ETO 5.0 mg/; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L pDST (MGIT960), gDST (whole genome sequencing), composite Genetic loci required for resistance testing criteria satisfied for isoniazid, fluoroquinolones, and amikacin gene targets: *katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, rpoB, gyrA, gyrB, rrs, eis* promoter		
Flow and timing			
Comparative			
Notes	The study was designed to assess the diagnostic accuracy of Xpert MTB/XDR as a reflex test to detect tuberculosis drug resistance, and not detection of pulmonary tuberculosis. The study population was previously positive for tuberculosis by Xpert MTB/RIF or Xpert MTB/RIF Ultra testing.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	

Penn-Nicholson 2021 Moldova *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Penn-Nicholson 2021 South Africa

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective Participants were prescreened for pulmonary tuberculosis symptoms and the presence of at least one risk factor for drug-resistant tuberculosis. Participants who met screening criteria received prior testing with Xpert MTB/RIF or Xpert MTB/RIF Ultra and those found to be Xpert MTB/RIF MTBC-positive or Xpert MTB/RIF Ultra MTBC-positive were enrolled. More than half of the population was also preselected for rifampicin resistance (and not just pulmonary tuberculosis). Screening was random and enrolment was consecutive and sequential for the two phases
Patient characteristics and setting	Presenting signs and symptoms: symptoms suggestive of pulmonary tuberculosis, i.e. persistent cough (≥ 2 weeks) or as per local definition of suspected pulmonary tuberculosis), and at least one of the following. - Previously received > 1 month of treatment for a prior tuberculosis episode or - Failing TB treatment with positive sputum smear or culture after ≥ 3 months of a standard TB treatment or - Had close contact with a known drug-resistant TB case or - Newly diagnosed with MDR-TB within the last 30 days or - Previously diagnosed with MDR-TB and failed TB treatment with positive sputum smear or culture after ≥ 3 months of a standard MDR-TB treatment regimen Exclusions for enrolment: sputum volume < 3 mL Age: ≥ 18 years; median 36 years (range 18 to 64) Sex, female: 29/82 (35%) HIV infection: 41/47 (87%) Previous TB treatment: 286 participants had received >1 month of treatment for a previous tuberculosis episode (in the full study) Sample size: 82; 61/82 (74%) with known rifampicin resistance Clinical setting: outpatient and inpatient in full study Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes
Index tests	Xpert MTB/XDR
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert MTB/RIF and Xpert Ultra Resistance to isoniazid, fluoroquinolones, moxifloxacin, levofloxacin, amikacin, kanamycin, capreomycin, ethionamide

Penn-Nicholson 2021 South Africa *(Continued)*

	INH 0.1 mg/L; MFX High 1.0 mg/L and Low 0.25 mg/L; LFX 1.0 mg/L; ETO 5.0 mg/L; AMK 1.0 mg/L; KAN 2.5 mg/L; CAP 2.5 mg/L pDST (MGIT 960), gDST (whole genome sequencing), composite Genetic loci required for resistance testing criteria satisfied for isoniazid, fluoroquinolones, and amikacin gene targets: *katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, rpoB, gyrA, gyrB, rrs, eis* promoter
Flow and timing	
Comparative	
Notes	The study was designed to assess the diagnostic accuracy of Xpert MTB/XDR as a reflex test to detect tuberculosis drug resistance, and not detection of pulmonary tuberculosis. The study population was previously positive for tuberculosis by Xpert MTB/RIF or Xpert MTB/RIF Ultra testing

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Penn-Nicholson 2021 South Africa *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Abbreviations: **AMK:** amikacin; **CAP:** capreomycin; **ETO:** ethionamide; **gDST:** genotypic drug susceptibility testing; **INH:** isoniazid; **KAN:** kanamycin; **LJ:** Löwenstein–Jensen medium;**LFX:** levofloxacin; **MDR-TB:** multidrug-resistant tuberculosis; **MFX:** moxifloxacin; **MGIT:** Mycobacteria Growth Indicator Tube;**MTB:** *Mycobacterium tuberculosis;* **NGS:** next-generation sequencing ; **OFX:** ofloxacin; **pDST:** phenotypic drug susceptibility testing; **RIF:** rifampicin;**TB:** tuberculosis**; XDR:** extensively drug-resistant.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andreevskaya 2020	Not the index test
Beutler 2020	Not a diagnostic accuracy study
Bisognin 2020	Not the index test
Broda 2018	Not the index test
Cao 2021	Combined clinical specimens and cultured isolates
Chakravorty 2017	Prototype test
Chang 2020	Not the index test

Study	Reason for exclusion
Chumpa 2020	Not the index test
Ciesielczuk 2020	Not the index test
Foongladda 2016	Not the index test
Galarza 2016	Not the index test
Georghiou 2021	Not a diagnotic study; analytical study
Han 2019	Extrapulmonary specimens
Havlicek 2018	Not the index test
Huang 2015	Not the index test
Kim 2019	Not the index test
Klotoe 2018	Not the index test
Law 2018	Not the index test
Lee 2015	Not the index test
Li 2017	Not the index test
Mokaddas 2019	Not the index test
Murray 2019	Not a diagnostic accuracy study
Pang 2016	Not the index test
Santos 2017	Not the index test
Shah 2019	Not the index test
Strydom 2015	Not the index test
Wang 2018	Not the index test
Xie 2017	Prototype test

Characteristics of ongoing studies *[ordered by study ID]*

NCT03303963

Study name	DIAgnostics for Multidrug Resistant Tuberculosis in Africa (DIAMA)
Target condition and reference standard(s)	Tuberculosis, Multidrug-Resistant
Index and comparator tests	Diagnostic Test: Deeplex test, MolBio TrueNat for 2nd line, GeneXpert 2nd line Diagnostic Test: Fluorescein DiAcetate (FDA) Microscopy, GeneXpert Ct value, pre-rRNA synthesis

NCT03303963 *(Continued)*

Starting date	4 May 2017
Contact information	affolabi_dissou@yahoo.fr
Notes	

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Xpert MTB/XDR, direct, TB detection, culture	3	1228
2 Xpert MTB/XDR, direct, smear-positive TB, culture	1	400
3 Xpert MTB/XDR, direct, smear-negative TB, culture	1	128
4 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, pDST	6	1083
5 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, gDST	6	999
6 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, composite	6	1055
7 Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, pDST	4	492
8 Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, gDST	4	434
9 Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, composite	4	476
10 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, pDST	6	1021
11 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, gDST	6	997
12 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, composite	6	1021
13 Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, pDST	4	491
14 Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, gDST	4	434
15 Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, composite	4	452

Test	No. of studies	No. of participants
16 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, pDST	5	835
17 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, gDST	6	1001
18 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, composite	5	843
19 Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, pDST	4	492
20 Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, gDST	4	434
21 Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, composite	4	457
22 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, pDST	6	1008
23 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, gDST	6	990
24 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, composite	6	1005
25 Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, pDST	4	490
26 Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, gDST	4	433
27 Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, composite	6	782
28 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, pDST	6	947
29 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, gDST	6	990
30 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, composite	6	1008
31 Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, pDST	4	491
32 Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, gDST	4	433
33 Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, composite	4	446
34 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, pDST	5	771
35 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, gDST	6	991
36 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, composite	5	823

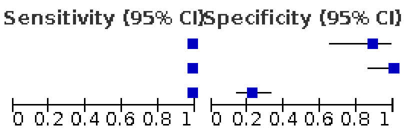
Test	No. of studies	No. of participants
37 Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, pDST	4	491
38 Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, gDST	4	434
39 Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, composite	4	444
40 Xpert MTB/XDR, direct, isoniazid, composite, direct comparison	1	564
41 Xpert MTB/XDR, indirect, isoniazid, composite, direct comparison	1	564
42 Xpert MTB/XDR, direct, fluoroquinolone, composite, direct comparison	1	530
43 Xpert MTB/XDR, indirect, fluoroquinolone, composite, direct comparison	1	530
44 Xpert MTB/XDR, direct, ethionamide, composite, direct comparison	1	541
45 Xpert MTB/XDR, indirect, ethionamide, composite, direct comparison	1	541
46 Xpert MTB/XDR, direct, amikacin, composite, direct comparison	1	509
47 Xpert MTB/XDR, indirect, amikacin, composite, direct comparison	1	509
48 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, isoniazid, composite	1	438
49 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, isoniazid, composite	1	137
50 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, fluoroquinolone, composite	1	410
51 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, fluoroquinolone, composite	1	134
52 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, ethionamide, composite	1	417
53 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, ethionamide, composite	1	132
54 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, amikacin, composite	1	404
55 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, amikacin, composite	1	130
56 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, isoniazid, composite	1	60
57 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, isoniazid, composite	1	340

Test	No. of studies	No. of participants
58 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, fluoroquinolone, composite	1	45
59 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, fluoroquinolone, composite	1	333
60 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, ethionamide, composite	1	53
61 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, ethionamide, composite	1	332
62 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, amikacin, composite	1	44
63 Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, amikacin, composite	1	317
64 Xpert MTB/XDR, direct, no previous treatment, isoniazid, composite	1	418
65 Xpert MTB/XDR, direct, previous treatment, isoniazid, composite	1	105
66 Xpert MTB/XDR, direct, no previous treatment, fluoroquinolone, composite	1	391
67 Xpert MTB/XDR, direct, previous treatment, fluoroquinolone, composite	1	100
68 Xpert MTB/XDR, direct, no previous treatment, ethionamide, composite	1	398
69 Xpert MTB/XDR, direct, previous treatment, ethionamide, composite	1	102
70 Xpert MTB/XDR, direct, no previous treatment, amikacin, composite	1	378
71 Xpert MTB/XDR, direct, previous treatment, amikacin, composite	1	94

Test 1. Xpert MTB/XDR, direct, TB detection, culture

Xpert MTB/XDR, direct, TB detection, culture

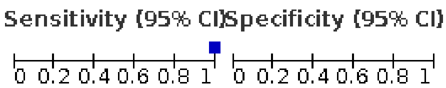
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	188	2	2	16	0.99 [0.96, 1.00]	0.89 [0.65, 0.99]
Omar 2020 South Africa	292	0	5	25	0.98 [0.96, 0.99]	1.00 [0.86, 1.00]
Penn-Nicholson 2021	599	69	10	20	0.98 [0.97, 0.99]	0.22 [0.14, 0.33]



Test 2. Xpert MTB/XDR, direct, smear-positive TB, culture

Xpert MTB/XDR, direct, smear-positive TB, culture

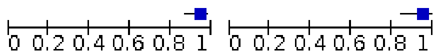
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020	398	0	2	0	0.99 [0.98, 1.00]	Not estimable



Test 3. Xpert MTB/XDR, direct, smear-negative TB, culture

Xpert MTB/XDR, direct, smear-negative TB, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020	80	2	5	41	0.94 [0.87, 0.98]	0.95 [0.84, 0.99]



Test 4. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, pDST

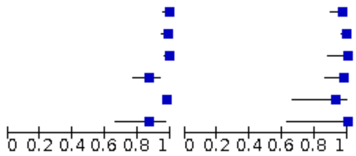
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	117	0	10	60	0.92 [0.86, 0.96]	1.00 [0.94, 1.00]
Omar 2020 South Africa	127	2	13	149	0.91 [0.85, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (Mumbai)	143	0	2	33	0.99 [0.95, 1.00]	1.00 [0.89, 1.00]
Penn-Nicholson 2021 India (New Delhi)	63	5	15	33	0.81 [0.70, 0.89]	0.87 [0.72, 0.96]
Penn-Nicholson 2021 Moldova	213	0	3	14	0.99 [0.96, 1.00]	1.00 [0.77, 1.00]
Penn-Nicholson 2021 South Africa	45	1	5	30	0.90 [0.78, 0.97]	0.97 [0.83, 1.00]

Test 5. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, gDST

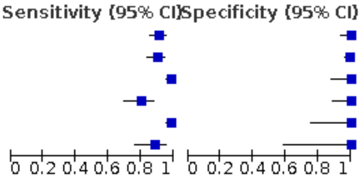
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	113	2	1	64	0.99 [0.95, 1.00]	0.97 [0.89, 1.00]
Omar 2020 South Africa	128	1	2	160	0.98 [0.95, 1.00]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	132	0	1	29	0.99 [0.96, 1.00]	1.00 [0.88, 1.00]
Penn-Nicholson 2021 India (New Delhi)	61	1	9	38	0.87 [0.77, 0.94]	0.97 [0.87, 1.00]
Penn-Nicholson 2021 Moldova	208	1	4	13	0.98 [0.95, 0.99]	0.93 [0.66, 1.00]
Penn-Nicholson 2021 South Africa	20	0	3	8	0.87 [0.66, 0.97]	1.00 [0.63, 1.00]



Test 6. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, isoniazid, composite

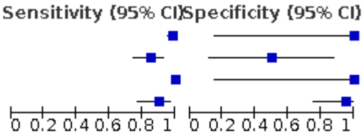
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	117	0	11	59	0.91 [0.85, 0.96]	1.00 [0.94, 1.00]
Omar 2020 South Africa	128	1	14	148	0.90 [0.84, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (Mumbai)	143	0	2	28	0.99 [0.95, 1.00]	1.00 [0.88, 1.00]
Penn-Nicholson 2021 India (New Delhi)	68	0	17	31	0.80 [0.70, 0.88]	1.00 [0.89, 1.00]
Penn-Nicholson 2021 Moldova	213	0	4	13	0.98 [0.95, 0.99]	1.00 [0.75, 1.00]
Penn-Nicholson 2021 South Africa	45	0	6	7	0.88 [0.76, 0.96]	1.00 [0.59, 1.00]



Test 7. Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, pDST

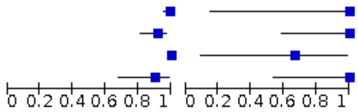
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	141	0	2	2	0.99 [0.95, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 India (New Delhi)	58	3	10	3	0.85 [0.75, 0.93]	0.50 [0.12, 0.88]
Penn-Nicholson 2021 Moldova	210	0	0	2	1.00 [0.98, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 South Africa	37	1	4	19	0.90 [0.77, 0.97]	0.95 [0.75, 1.00]



Test 8. Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, gDST

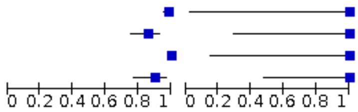
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	130	0	1	2	0.99 [0.96, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 India (New Delhi)	54	0	5	7	0.92 [0.81, 0.97]	1.00 [0.59, 1.00]
Penn-Nicholson 2021 Moldova	206	1	0	2	1.00 [0.98, 1.00]	0.67 [0.09, 0.99]
Penn-Nicholson 2021 South Africa	18	0	2	6	0.90 [0.68, 0.99]	1.00 [0.54, 1.00]



Test 9. Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, isoniazid, composite

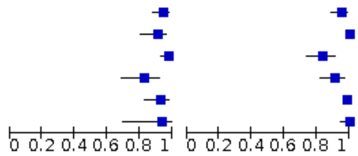
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	141	0	2	1	0.99 [0.95, 1.00]	1.00 [0.03, 1.00]
Penn-Nicholson 2021 India (New Delhi)	61	0	10	3	0.86 [0.76, 0.93]	1.00 [0.29, 1.00]
Penn-Nicholson 2021 Moldova	210	0	0	2	1.00 [0.98, 1.00]	1.00 [0.16, 1.00]
Penn-Nicholson 2021 South Africa	37	0	4	5	0.90 [0.77, 0.97]	1.00 [0.48, 1.00]



Test 10. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, pDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, pDST

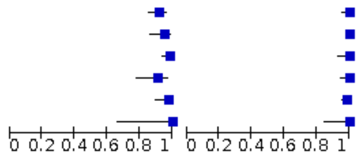
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	90	4	5	87	0.95 [0.88, 0.98]	0.96 [0.89, 0.99]
Omar 2020 South Africa	58	0	6	167	0.91 [0.81, 0.96]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	102	12	2	62	0.98 [0.93, 1.00]	0.84 [0.73, 0.91]
Penn-Nicholson 2021 India (New Delhi)	38	6	8	64	0.83 [0.69, 0.92]	0.91 [0.82, 0.97]
Penn-Nicholson 2021 Moldova	52	2	4	172	0.93 [0.83, 0.98]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	15	0	1	64	0.94 [0.70, 1.00]	1.00 [0.94, 1.00]



Test 11. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, gDST

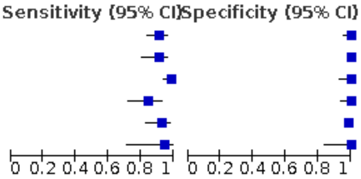
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	94	0	8	78	0.92 [0.85, 0.97]	1.00 [0.95, 1.00]
Omar 2020 South Africa	58	0	3	228	0.95 [0.86, 0.99]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	107	0	2	53	0.98 [0.94, 1.00]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 India (New Delhi)	39	0	4	66	0.91 [0.78, 0.97]	1.00 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	50	3	1	172	0.98 [0.90, 1.00]	0.98 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	9	0	0	22	1.00 [0.66, 1.00]	1.00 [0.85, 1.00]



Test 12. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, fluoroquinolone, composite

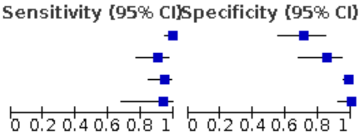
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	94	0	9	83	0.91 [0.84, 0.96]	1.00 [0.96, 1.00]
Omar 2020 South Africa	58	0	6	225	0.91 [0.81, 0.96]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	113	0	2	53	0.98 [0.94, 1.00]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 India (New Delhi)	44	0	8	61	0.85 [0.72, 0.93]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	52	2	4	169	0.93 [0.83, 0.98]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	16	0	1	21	0.94 [0.71, 1.00]	1.00 [0.84, 1.00]



Test 13. Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, pDST

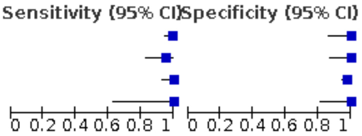
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	102	12	1	30	0.99 [0.95, 1.00]	0.71 [0.55, 0.84]
Penn-Nicholson 2021 India (New Delhi)	37	5	4	28	0.90 [0.77, 0.97]	0.85 [0.68, 0.95]
Penn-Nicholson 2021 Moldova	51	2	3	156	0.94 [0.85, 0.99]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 South Africa	14	0	1	45	0.93 [0.68, 1.00]	1.00 [0.92, 1.00]



Test 14. Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, gDST

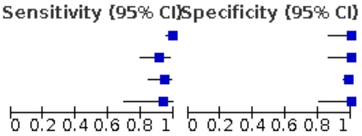
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	107	0	1	25	0.99 [0.95, 1.00]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 India (New Delhi)	37	0	2	27	0.95 [0.83, 0.99]	1.00 [0.87, 1.00]
Penn-Nicholson 2021 Moldova	50	3	0	156	1.00 [0.93, 1.00]	0.98 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	8	0	0	18	1.00 [0.63, 1.00]	1.00 [0.81, 1.00]



Test 15. Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, fluoroquinolone, composite

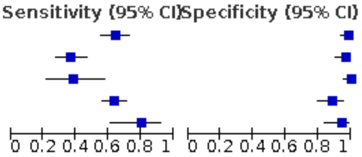
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	113	0	1	25	0.99 [0.95, 1.00]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 India (New Delhi)	42	0	4	25	0.91 [0.79, 0.98]	1.00 [0.86, 1.00]
Penn-Nicholson 2021 Moldova	51	2	3	153	0.94 [0.85, 0.99]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 South Africa	15	0	1	17	0.94 [0.70, 1.00]	1.00 [0.80, 1.00]



Test 16. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, pDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, pDST

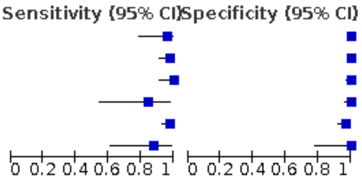
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	75	2	41	112	0.65 [0.55, 0.73]	0.98 [0.94, 1.00]
Penn-Nicholson 2021 India (Mumbai)	39	2	66	71	0.37 [0.28, 0.47]	0.97 [0.90, 1.00]
Penn-Nicholson 2021 India (New Delhi)	12	0	19	85	0.39 [0.22, 0.58]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	101	8	57	64	0.64 [0.56, 0.71]	0.89 [0.79, 0.95]
Penn-Nicholson 2021 South Africa	24	3	6	48	0.80 [0.61, 0.92]	0.94 [0.84, 0.99]



Test 17. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, gDST

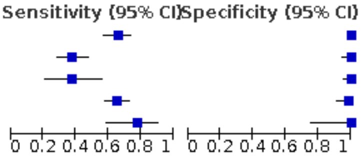
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	23	0	1	157	0.96 [0.79, 1.00]	1.00 [0.98, 1.00]
Omar 2020 South Africa	81	0	2	209	0.98 [0.92, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	39	0	0	123	1.00 [0.91, 1.00]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	11	0	2	96	0.85 [0.55, 0.98]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	103	4	2	117	0.98 [0.93, 1.00]	0.97 [0.92, 0.99]
Penn-Nicholson 2021 South Africa	14	0	2	15	0.88 [0.62, 0.98]	1.00 [0.78, 1.00]



Test 18. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, ethionamide, composite

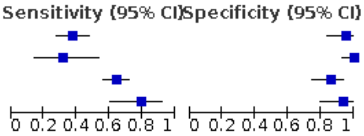
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	81	0	42	169	0.66 [0.57, 0.74]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	40	0	66	63	0.38 [0.29, 0.48]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	12	0	20	78	0.38 [0.21, 0.56]	1.00 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	108	1	57	62	0.65 [0.58, 0.73]	0.98 [0.91, 1.00]
Penn-Nicholson 2021 South Africa	24	0	7	13	0.77 [0.59, 0.90]	1.00 [0.75, 1.00]



Test 19. Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, pDST

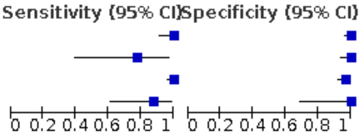
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	39	2	65	39	0.38 [0.28, 0.48]	0.95 [0.83, 0.99]
Penn-Nicholson 2021 India (New Delhi)	8	0	17	49	0.32 [0.15, 0.54]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	100	8	55	49	0.65 [0.56, 0.72]	0.86 [0.74, 0.94]
Penn-Nicholson 2021 South Africa	23	2	6	30	0.79 [0.60, 0.92]	0.94 [0.79, 0.99]



Test 20. Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, gDST

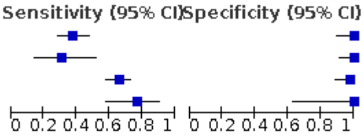
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	39	0	0	94	1.00 [0.91, 1.00]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	2	57	0.78 [0.40, 0.97]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	103	3	0	103	1.00 [0.96, 1.00]	0.97 [0.92, 0.99]
Penn-Nicholson 2021 South Africa	14	0	2	10	0.88 [0.62, 0.98]	1.00 [0.69, 1.00]



Test 21. Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, ethionamide, composite

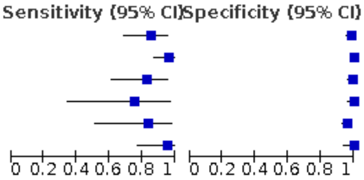
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	40	0	65	35	0.38 [0.29, 0.48]	1.00 [0.90, 1.00]
Penn-Nicholson 2021 India (New Delhi)	8	0	18	42	0.31 [0.14, 0.52]	1.00 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	107	1	55	48	0.66 [0.58, 0.73]	0.98 [0.89, 1.00]
Penn-Nicholson 2021 South Africa	23	0	7	8	0.77 [0.58, 0.90]	1.00 [0.63, 1.00]



Test 22. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, pDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, pDST

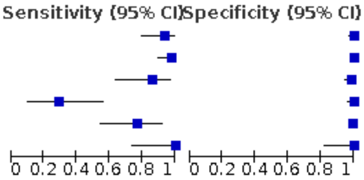
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	29	2	5	141	0.85 [0.69, 0.95]	0.99 [0.95, 1.00]
Omar 2020 South Africa	50	0	2	176	0.96 [0.87, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	153	0.83 [0.61, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	2	107	0.75 [0.35, 0.97]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 Moldova	10	8	2	210	0.83 [0.52, 0.98]	0.96 [0.93, 0.98]
Penn-Nicholson 2021 South Africa	21	0	1	59	0.95 [0.77, 1.00]	1.00 [0.94, 1.00]



Test 23. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, gDST

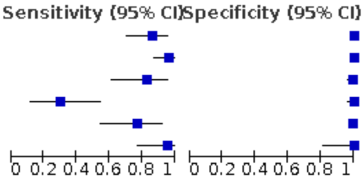
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	31	0	2	144	0.94 [0.80, 0.99]	1.00 [0.97, 1.00]
Omar 2020 South Africa	50	0	1	235	0.98 [0.90, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	18	2	3	138	0.86 [0.64, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	12	92	0.29 [0.10, 0.56]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	203	0.77 [0.55, 0.92]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	19	1.00 [0.74, 1.00]	1.00 [0.82, 1.00]



Test 24. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, amikacin, composite

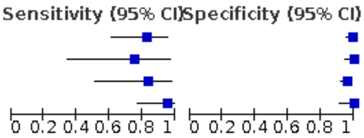
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	31	0	5	147	0.86 [0.71, 0.95]	1.00 [0.98, 1.00]
Omar 2020 South Africa	50	0	2	234	0.96 [0.87, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	137	0.83 [0.61, 0.95]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	14	89	0.30 [0.12, 0.54]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	203	0.77 [0.55, 0.92]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	18	0.95 [0.77, 1.00]	1.00 [0.81, 1.00]



Test 25. Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, pDST

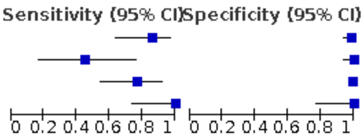
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	1	4	120	0.83 [0.61, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	2	65	0.75 [0.35, 0.97]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	10	8	2	192	0.83 [0.52, 0.98]	0.96 [0.92, 0.98]
Penn-Nicholson 2021 South Africa	21	0	1	39	0.95 [0.77, 1.00]	1.00 [0.91, 1.00]



Test 26. Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, gDST

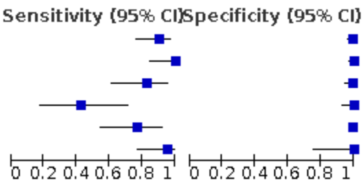
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	18	2	3	109	0.86 [0.64, 0.97]	0.98 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	6	55	0.45 [0.17, 0.77]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	186	0.77 [0.55, 0.92]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]



Test 27. Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, amikacin, composite

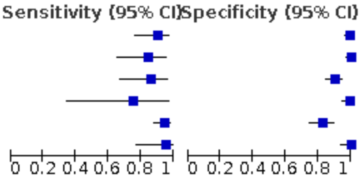
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	36	1	4	136	0.90 [0.76, 0.97]	0.99 [0.96, 1.00]
Omar 2020 South Africa	22	0	0	140	1.00 [0.85, 1.00]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	1	4	108	0.83 [0.61, 0.95]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	8	53	0.43 [0.18, 0.71]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	17	1	5	186	0.77 [0.55, 0.92]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]



Test 28. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, pDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, pDST

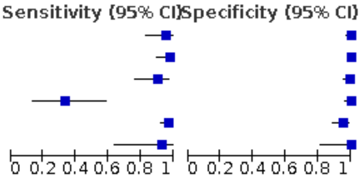
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	36	1	4	136	0.90 [0.76, 0.97]	0.99 [0.96, 1.00]
Omar 2020 South Africa	22	0	4	140	0.85 [0.65, 0.96]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	24	14	4	135	0.86 [0.67, 0.96]	0.91 [0.85, 0.95]
Penn-Nicholson 2021 India (New Delhi)	6	1	2	107	0.75 [0.35, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	111	19	7	93	0.94 [0.88, 0.98]	0.83 [0.75, 0.89]
Penn-Nicholson 2021 South Africa	21	0	1	59	0.95 [0.77, 1.00]	1.00 [0.94, 1.00]



Test 29. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, gDST

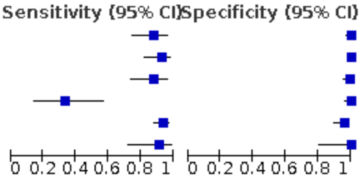
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	37	0	2	138	0.95 [0.83, 0.99]	1.00 [0.97, 1.00]
Omar 2020 South Africa	51	0	1	234	0.98 [0.90, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	36	1	4	120	0.90 [0.76, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	12	91	0.33 [0.13, 0.59]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	123	5	4	94	0.97 [0.92, 0.99]	0.95 [0.89, 0.98]
Penn-Nicholson 2021 South Africa	12	0	1	18	0.92 [0.64, 1.00]	1.00 [0.81, 1.00]



Test 30. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, composite

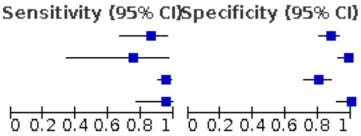
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	37	0	5	141	0.88 [0.74, 0.96]	1.00 [0.97, 1.00]
Omar 2020 South Africa	51	0	4	231	0.93 [0.82, 0.98]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	36	1	5	119	0.88 [0.74, 0.96]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	14	89	0.33 [0.15, 0.57]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	126	4	9	89	0.93 [0.88, 0.97]	0.96 [0.89, 0.99]
Penn-Nicholson 2021 South Africa	21	0	2	17	0.91 [0.72, 0.99]	1.00 [0.80, 1.00]



Test 31. Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, pDST

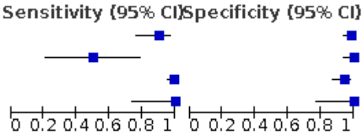
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	24	14	4	102	0.86 [0.67, 0.96]	0.88 [0.81, 0.93]
Penn-Nicholson 2021 India (New Delhi)	6	1	2	65	0.75 [0.35, 0.97]	0.98 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	109	19	5	79	0.96 [0.90, 0.99]	0.81 [0.71, 0.88]
Penn-Nicholson 2021 South Africa	21	0	1	39	0.95 [0.77, 1.00]	1.00 [0.91, 1.00]



Test 32. Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, gDST

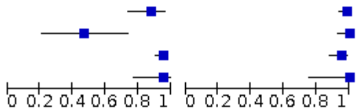
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	36	1	4	91	0.90 [0.76, 0.97]	0.99 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	6	54	0.50 [0.21, 0.79]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	121	5	1	82	0.99 [0.96, 1.00]	0.94 [0.87, 0.98]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]



Test 33. Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, composite

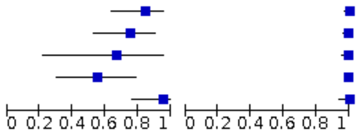
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	36	1	5	90	0.88 [0.74, 0.96]	0.99 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	8	53	0.47 [0.21, 0.73]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	124	4	6	77	0.95 [0.90, 0.98]	0.95 [0.88, 0.99]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]



Test 34. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, pDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, pDST

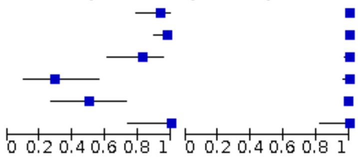
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	21	0	4	142	0.84 [0.64, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	18	1	6	153	0.75 [0.53, 0.90]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	4	1	2	109	0.67 [0.22, 0.96]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	10	1	8	211	0.56 [0.31, 0.78]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	20	0	1	59	0.95 [0.76, 1.00]	1.00 [0.94, 1.00]



Test 35. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, gDST

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, gDST

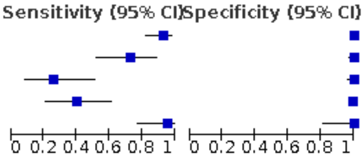
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	29	0	2	146	0.94 [0.79, 0.99]	1.00 [0.98, 1.00]
Omar 2020 South Africa	49	0	1	236	0.98 [0.89, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	0	4	139	0.83 [0.61, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	12	92	0.29 [0.10, 0.56]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	10	1	10	205	0.50 [0.27, 0.73]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	19	1.00 [0.74, 1.00]	1.00 [0.82, 1.00]



Test 36. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, composite

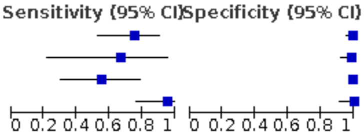
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	49	0	4	233	0.92 [0.82, 0.98]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	0	7	136	0.73 [0.52, 0.88]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	14	90	0.26 [0.09, 0.51]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	10	1	15	200	0.40 [0.21, 0.61]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	18	0.95 [0.77, 1.00]	1.00 [0.81, 1.00]



Test 37. Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, pDST

Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, pDST

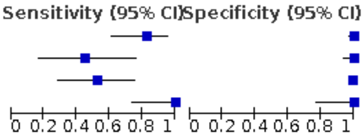
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	18	1	6	120	0.75 [0.53, 0.90]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	4	1	2	67	0.67 [0.22, 0.96]	0.99 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	10	1	8	193	0.56 [0.31, 0.78]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	20	0	1	39	0.95 [0.76, 1.00]	1.00 [0.91, 1.00]



Test 38. Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, gDST

Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, gDST

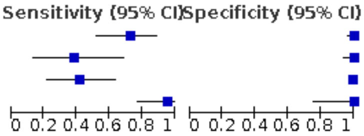
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	0	4	110	0.83 [0.61, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	6	55	0.45 [0.17, 0.77]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	10	1	9	189	0.53 [0.29, 0.76]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]



Test 39. Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, composite

Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, composite

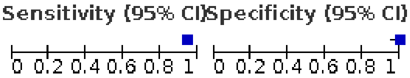
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	0	7	107	0.73 [0.52, 0.88]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	8	54	0.38 [0.14, 0.68]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	10	1	14	184	0.42 [0.22, 0.63]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]



Test 40. Xpert MTB/XDR, direct, isoniazid, composite, direct comparison

Xpert MTB/XDR, direct, isoniazid, composite, direct comparison

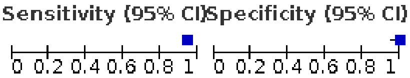
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	459	0	28	77	0.94 [0.92, 0.96]	1.00 [0.95, 1.00]



Test 41. Xpert MTB/XDR, indirect, isoniazid, composite, direct comparison

Xpert MTB/XDR, indirect, isoniazid, composite, direct comparison

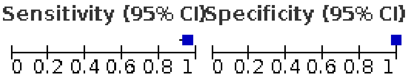
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	461	0	26	77	0.95 [0.92, 0.96]	1.00 [0.95, 1.00]



Test 42. Xpert MTB/XDR, direct, fluoroquinolone, composite, direct comparison

Xpert MTB/XDR, direct, fluoroquinolone, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	222	2	12	294	0.95 [0.91, 0.97]	0.99 [0.98, 1.00]



Test 43. Xpert MTB/XDR, indirect, fluoroquinolone, composite, direct comparison

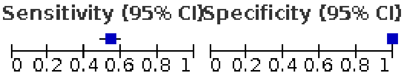
Xpert MTB/XDR, indirect, fluoroquinolone, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	224	0	10	296	0.96 [0.92, 0.98]	1.00 [0.99, 1.00]

Test 44. Xpert MTB/XDR, direct, ethionamide, composite, direct comparison

Xpert MTB/XDR, direct, ethionamide, composite, direct comparison

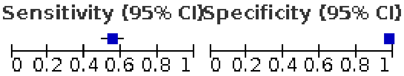
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	178	1	150	212	0.54 [0.49, 0.60]	1.00 [0.97, 1.00]



Test 45. Xpert MTB/XDR, indirect, ethionamide, composite, direct comparison

Xpert MTB/XDR, indirect, ethionamide, composite, direct comparison

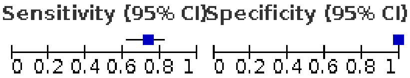
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	182	4	146	209	0.55 [0.50, 0.61]	0.98 [0.95, 0.99]



Test 46. Xpert MTB/XDR, direct, amikacin, composite, direct comparison

Xpert MTB/XDR, direct, amikacin, composite, direct comparison

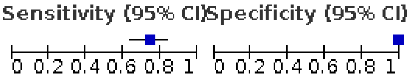
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	60	2	22	425	0.73 [0.62, 0.82]	1.00 [0.98, 1.00]



Test 47. Xpert MTB/XDR, indirect, amikacin, composite, direct comparison

Xpert MTB/XDR, indirect, amikacin, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	61	1	21	426	0.74 [0.64, 0.83]	1.00 [0.99, 1.00]



Test 48. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, isoniazid, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	362	0	22	54	0.94 [0.91, 0.96]	1.00 [0.93, 1.00]

Test 49. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, isoniazid, composite

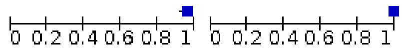
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	105	0	7	25	0.94 [0.88, 0.97]	1.00 [0.86, 1.00]

Test 50. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, fluoroquinolone, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, fluoroquinolone, composite

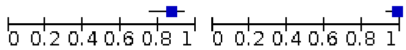
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	171	1	7	231	0.96 [0.92, 0.98]	1.00 [0.98, 1.00]



Test 51. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, fluoroquinolone, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, fluoroquinolone, composite

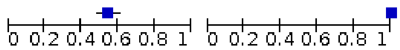
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	52	1	8	73	0.87 [0.75, 0.94]	0.99 [0.93, 1.00]



Test 52. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, ethionamide, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, ethionamide, composite

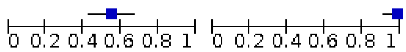
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	143	0	118	156	0.55 [0.49, 0.61]	1.00 [0.98, 1.00]



Test 53. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, ethionamide, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, ethionamide, composite

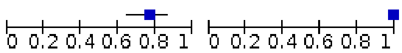
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	39	1	32	60	0.55 [0.43, 0.67]	0.98 [0.91, 1.00]



Test 54. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, amikacin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, amikacin, composite

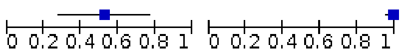
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	52	1	16	335	0.76 [0.65, 0.86]	1.00 [0.98, 1.00]



Test 55. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, amikacin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, amikacin, composite

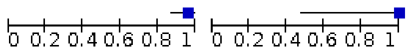
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	9	1	8	112	0.53 [0.28, 0.77]	0.99 [0.95, 1.00]



Test 56. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, isoniazid, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, isoniazid, composite

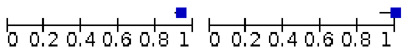
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	53	0	2	5	0.96 [0.87, 1.00]	1.00 [0.48, 1.00]



Test 57. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, isoniazid, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, isoniazid, composite

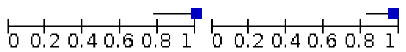
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	275	0	19	46	0.94 [0.90, 0.96]	1.00 [0.92, 1.00]



Test 58. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, fluoroquinolone, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, fluoroquinolone, composite

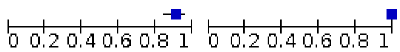
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	15	1	0	29	1.00 [0.78, 1.00]	0.97 [0.83, 1.00]



Test 59. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, fluoroquinolone, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, fluoroquinolone, composite

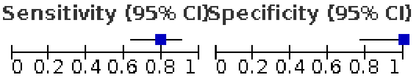
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	111	1	11	210	0.91 [0.84, 0.95]	1.00 [0.97, 1.00]



Test 60. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, ethionamide, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, ethionamide, composite

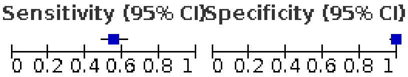
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	31	0	8	14	0.79 [0.64, 0.91]	1.00 [0.77, 1.00]



Test 61. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, ethionamide, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, ethionamide, composite

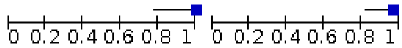
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	109	1	87	135	0.56 [0.48, 0.63]	0.99 [0.96, 1.00]



Test 62. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, amikacin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, amikacin, composite

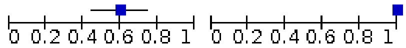
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	15	1	0	28	1.00 [0.78, 1.00]	0.97 [0.82, 1.00]



Test 63. Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, amikacin, composite

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, amikacin, composite

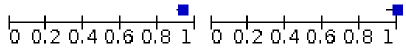
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	27	0	18	272	0.60 [0.44, 0.74]	1.00 [0.99, 1.00]



Test 64. Xpert MTB/XDR, direct, no previous treatment, isoniazid, composite

Xpert MTB/XDR, direct, no previous treatment, isoniazid, composite

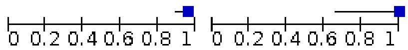
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	333	0	23	62	0.94 [0.90, 0.96]	1.00 [0.94, 1.00]



Test 65. Xpert MTB/XDR, direct, previous treatment, isoniazid, composite

Xpert MTB/XDR, direct, previous treatment, isoniazid, composite

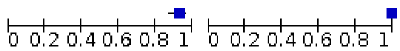
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	92	0	4	9	0.96 [0.90, 0.99]	1.00 [0.66, 1.00]



Test 66. Xpert MTB/XDR, direct, no previous treatment, fluoroquinolone, composite

Xpert MTB/XDR, direct, no previous treatment, fluoroquinolone, composite

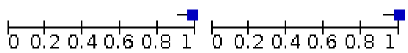
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	141	2	11	237	0.93 [0.87, 0.96]	0.99 [0.97, 1.00]



Test 67. Xpert MTB/XDR, direct, previous treatment, fluoroquinolone, composite

Xpert MTB/XDR, direct, previous treatment, fluoroquinolone, composite

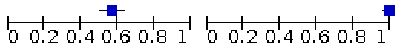
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	53	0	1	46	0.98 [0.90, 1.00]	1.00 [0.92, 1.00]



Test 68. Xpert MTB/XDR, direct, no previous treatment, ethionamide, composite

Xpert MTB/XDR, direct, no previous treatment, ethionamide, composite

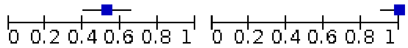
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	136	1	102	159	0.57 [0.51, 0.64]	0.99 [0.97, 1.00]		



Test 69. Xpert MTB/XDR, direct, previous treatment, ethionamide, composite

Xpert MTB/XDR, direct, previous treatment, ethionamide, composite

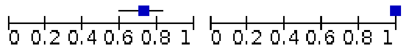
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	35	0	31	36	0.53 [0.40, 0.65]	1.00 [0.90, 1.00]		



Test 70. Xpert MTB/XDR, direct, no previous treatment, amikacin, composite

Xpert MTB/XDR, direct, no previous treatment, amikacin, composite

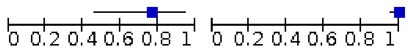
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	45	2	17	314	0.73 [0.60, 0.83]	0.99 [0.98, 1.00]		



Test 71. Xpert MTB/XDR, direct, previous treatment, amikacin, composite

Xpert MTB/XDR, direct, previous treatment, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	10	0	3	81	0.77 [0.46, 0.95]	1.00 [0.96, 1.00]		



ADDITIONAL TABLES

Table 1. Selected characteristics of included studies

Study year	Study cohorts (high MDR burden country?)	Study design	Laboratory level	№ of participants for analyses of drug resistance detection (% with rifampicin resistance)	Median age (range)	PLHIV	Reference standard for drug resistance	Loci included in gDST reference standard
Omar 2020 [a,b]	China (yes) South Africa (yes)	Cross-sectional	Central	530 (47.9%)	(13 to > 80 years)[b]	NR	pDST, gDST, composite	*katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, gyrA, gyrB, rrs, eis* promoter
Penn-Nicholson 2021 [a]	Moldova (yes); Mumbai (yes); New Delhi) (yes); South Africa (yes)	Cross-sectional	Central	611 (80.9%)	37 years (18 to 77 years)	16%	pDST, gDST, composite	*katG, inhA* promoter, *oxyR-ahpC* intergenic region, *fabG1, gyrA, gyrB, rrs, eis* promoter

Abbreviations: **gDST:** genotypic drug susceptibility testing; **MDR:** multidrug-resistant tuberculosis; **№:** number;**NR:** not reported; **pDST:** phenotypic drug susceptibility testing; **PLHIV:** people living with HIV.

[a]Characteristics of the individual study centres are provided in Characteristics of included studies.

[b]One participant was 13 years old; all other participants were 15 years and older.

Table 2. Xpert MTB/XDR summary sensitivity and specificity for resistance to tuberculosis drugs

Analysis group	Reference standard	Number of studies; number of study cohorts (participants)	№(%) with drug resistance	Summary sensitivity % (95% CI)	Summary specificity % (95% CI)	Positive predictive value % (95% CI)*	Negative predictive value % (95% CI)*
Irrespective of rifampicin resistance							
Isoniazid	pDST	2 studies; 6 study cohorts (1083)	756 (69.8)	94.2 (87.5 to 97.4)	98.5 (92.6 to 99.7)	76.9 (38.8 to 94.6)	99.7 (99.4 to 99.9)
Isoniazid	gDST	2 studies; 6 study cohorts (999)	682 (68.3)	97.3 (92.8 to 99.0)	98.4 (95.9 to 99.3)	75.6 (55.4 to 88.6)	99.9 (99.6 to 100)
Isoniazid	Composite	2 studies; 6 study cohorts (1055)	768 (72.8)	93.5 (86.5 to 97.0)	99.7 (96.6 to 100.0)	94.2 (58.6 to 99.5)	99.7 (99.3 to 99.8)
With rifampicin resistance							
Isoniazid	pDST	1 study; 4 study cohorts (492)	462 (93.9)	97.6 (84.4 to 99.7)	89.0 (50.2 to 98.5)	79.2 (34.2 to 96.5)	99.2 (94.5 to 99.9)

Table 2. Xpert MTB/XDR summary sensitivity and specificity for resistance to tuberculosis drugs *(Continued)*

Isoniazid	gDST	1 study; 4 study cohorts (434)	416 (95.9)	98.4 (88.9 to 99.8)	97.5 (27.1 to 100.0)	94.5 (15.4 to 99.9)	99.5 (96.6 to 99.9)
Isoniazid	Composite	1 study; 4 study cohorts (476)	465 (97.7)	97.6 (84.7 to 99.7)	100.0 (NE to 100.0)	100.0 (0.0 to NE)	99.3 (95.2 to 99.9)
Irrespective of rifampicin resistance							
Fluoro-quinolones	pDST	2 studies; 6 study cohorts (1021)	381 (37.3)	93.2 (88.1 to 96.2)	98.0 (90.8 to 99.6)	70.6 (34.0 to 91.8)	99.7 (99.4 to 99.8)
Fluoro-quinolones	gDST	2 studies; 6 study cohorts (997)	375 (37.6)	95.7 (91.8 to 97.7)	99.9 (92.0 to 100.0)	97.5 (36.9 to 100.0)	99.8 (99.6 to 99.9)
Fluoro-quinolones	Composite	2 studies; 6 study cohorts (1021)	407 (39.9)	92.8 (88.1 to 95.8)	99.8 (96.0 to 100.0)	95.5 (54.4 to 99.7)	99.6 (99.4 to 99.8)
With rifampicin resistance							
Fluoro-quinolones	pDST	1 study; 4 study cohorts (491)	213 (43.4)	95.4 (89.4 to 98.1)	95.3 (75.3 to 99.3)	89.7 (59.2 to 98.1)	98.6 (96.8 to 99.4)
Fluoro-quinolones	gDST	1 study; 4 study cohorts (434)	205 (47.2)	98.6 (94.3 to 99.7)	98.8 (94.7 to 99.7)	97.2 (88.6 to 99.4)	99.6 (98.2 to 99.9)
Fluoro-quinolones	Composite	1 study; 4 study cohorts (452)	230 (50.9)	96.0 (90.6 to 98.4)	99.1 (96.2 to 99.8)	97.9 (91.3 to 99.5)	98.8 (97.2 to 99.5)
Irrespective of rifampicin resistance							
Ethionamide	pDST	2 studies; 6 study cohorts (835)	440 (52.7)	56.6 (41.8 to 70.3)	97.1 (91.9 to 99.0)	50.9 (28.6 to 72.8)	97.8 (97.0 to 98.4)
Ethionamide	gDST	2 studies; 6 study cohorts (1001)	280 (28.0)	96.4 (92.2 to 98.3)	100.0 (82.5 to 100.0)	99.6 (19.5 to 100.0)	96.5 (92.7 to 98.4)
Ethionamide	Composite	2 studies; 6 study cohorts (843)	481 (47.0)	57.1 (42.8 to 70.2)	99.8 (95.3 to 100.0)	94.7 (39.9 to 99.8)	97.9 (97.1 to 98.5)
With rifampicin resistance							
Ethionamide	pDST	1 study; 4 study cohorts (492)	313 (63.6)	51.7 (33.1 to 69.8)	94.8 (84.8 to 98.3)	81.0 (62.2 to 91.7)	86.7 (81.9 to 90.4)

Table 2. Xpert MTB/XDR summary sensitivity and specificity for resistance to tuberculosis drugs *(Continued)*

Ethionamide	gDST	1 study; 4 study cohorts (434)	167 (38.5)	98.0 (74.2 to 99.9)	99.7 (83.5 to 100.0)	99.3 (68.6 to 100.0)	99.4 (91.2 to 100.0)
Ethionamide	Composite	1 study; 4 study cohorts (457)	323 (70.7)	53.1 (34.7 to 70.7)	99.5 (87.0 to 100.0)	98.0 (63.9 to 99.9)	87.6 (82.6 to 91.3)
Irrespective of rifampicin resistance							
Amikacin	pDST	2 studies; 6 study cohorts (1008)	151 (15.0)	89.1 (80.8 to 94.1)	99.5 (96.9 to 99.9)	90.1 (59.0 to 98.3)	99.5 (99.0 to 99.7)
Amikacin	gDST	2 studies; 6 study cohorts (990)	156 (15.8)	89.5 (64.5 to 97.6)	99.7 (98.4 to 99.9)	93.3 (73.9 to 98.6)	99.5 (97.9 to 99.9)
Amikacin	Composite	2 studies; 6 study cohorts (1005)	175 (17.4)	84.1 (63.0 to 94.3)	99.8 (99.0 to 99.9)	94.9 (81.1 to 98.8)	99.2 (98.0 to 99.7)
With rifampicin resistance							
Amikacin	pDST	1 study; 4 study cohorts (490)	65 (13.3)	86.1 (75.0 to 92.7)	98.9 (93.0 to 99.8)	97.2 (83.4 to 99.6)	95.9 (92.7 to 97.8)
Amikacin	gDST	1 study; 4 study cohorts (433)	66 (15.2)	81.1 (56.0 to 93.6)	99.2 (96.9 to 99.8)	97.8 (92.4 to 99.4)	94.6 (86.8 to 97.9)
Amikacin	Composite	1 study; 4 study cohorts (443)	81 (18.3)	79.0 (55.4 to 91.9)	99.5 (97.6 to 99.9)	98.4 (93.7 to 99.6)	94.0 (86.8 to 97.4)
Irrespective of rifampicin resistance							
Kanamycin	pDST	2 studies; 6 study cohorts (947)	40 (4.22)	90.0 (84.5 to 93.7)	98.6 (91.7 to 99.8)	77.5 (35.7 to 95.5)	99.5 (99.2 to 99.7)
Kanamycin	gDST	2 studies; 6 study cohorts (990)	39 (3.94)	91.7 (74.8 to 97.6)	99.8 (95.8 to 100.0)	96.1 (53.1 to 99.8)	99.6 (98.6 to 99.9)
Kanamycin	Composite	2 studies; 6 study cohorts (1008)	42 (4.17)	85.6 (70.3 to 93.7)	99.9 (93.2 to 100.0)	98.0 (40.0 to 100.0)	99.3 (98.4 to 99.7)
With rifampicin resistance							
Kanamycin	pDST	1 study; 4 study cohorts (491)	28 (5.70)	91.5 (83.1 to 96.0)	94.5 (79.5 to 98.7)	87.7 (63.9 to 96.7)	97.4 (94.8 to 98.7)
Kanamycin	gDST	1 study; 4 study cohorts (433)	40 (9.24)	93.8 (66.5 to 99.1)	98.6 (91.9 to 99.8)	96.7 (83.6 to 99.4)	98.1 (88.9 to 99.7)
Kanamycin	Composite	1 study; 4 study cohorts (446)	41 (9.19)	87.4 (66.0 to 96.1)	98.8 (91.2 to 99.9)	97.0 (81.6 to 99.6)	96.3 (89.7 to 98.7)
Irrespective of rifampicin resistance							

Table 2. Xpert MTB/XDR summary sensitivity and specificity for resistance to tuberculosis drugs *(Continued)*

Capreomycin	pDST	2 studies; 5 study cohorts (771)	25 (3.24)	78.2 (62.4 to 88.6)	99.6 (98.5 to 99.9)	91.4 (72.1 to 97.8)	98.9 (98.0 to 99.4)
Capreomycin	gDST	2 studies; 6 study cohorts (991)	31 (3.13)	86.5 (55.2 to 97.1)	99.9 (99.2 to 100.0)	99.5 (82.0 to 100.0)	93.1 (82.7 to 97.5)
Capreomycin	Composite	2 studies; 5 study cohorts (823)	53 (6.44)	73.1 (39.8 to 91.7)	99.9 (96.6 to 100.0)	98.2 (48.8 to 100.0)	98.7 (96.4 to 98.7)
With rifampicin resistance							
Capreomycin	pDST	1 study; 4 study cohorts (491)	24 (4.89)	76.5 (55.7 to 89.4)	99.3 (97.6 to 99.8)	97.9 (92.9 to 99.4)	93.4 (87.2 to 96.7)
Capreomycin	gDST	1 study; 4 study cohorts (434)	23 (5.30)	75.4 (43.6 to 92.4)	99.9 (93.9 to 100.0)	99.5 (82.0 to 100)	93.1 (82.7 to 97.5)
Capreomycin	Composite	1 study; 4 study cohorts (444)	26 (5.86)	67.2 (35.9 to 88.2)	99.7 (98.1 to 100.0)	99.0 (93.4 to 99.9)	91.0 (80.9 to 96.0)

Abbreviations: **CI:** confidence interval; **gDST:** genotypic drug susceptibility testing; **NE:** not estimable; **№**: number; **pDST:** phenotypic drug susceptibility testing.
Study cohorts were treated as distinct units in the meta-analyses.
*Prevalence for calculating predictive values: 5% in people irrespective of rifampicin resistance and 30% in people with known rifampicin resistance.

Table 3. Summary proportion of Xpert XDR/MTB indeterminate results by drug

Drug	Study	Total	№ indeterminate	Summary proportion (95% CI)
Isoniazid	Omar 2020	498	2	0.34% (0.00 to 0.68)
	Penn-Nicholson 2021	657	2	
Fluoro-quinolones	Omar 2020	498	4	1.05% (0.46 to 1.64)
	Penn-Nicholson 2021	657	9	
Ethionamide	Omar 2020	498	0	0.06% (0.00 to 0.34)
	Penn-Nicholson 2021	657	1	
Amikacin	Omar 2020	498	8	2.33% (1.46 to 3.20)
	Penn-Nicholson 2021	657	23	

Abbreviations: **CI:** confidence interval; **№**: number.

Table 4. Xpert MTB/XDR summary sensitivity and specificity for resistance to isoniazid and fluoroquinolones, sensitivity analyses

Analysis group	Number of studies and number of study cohorts (participants)	№ (%) with drug resistance	Summary sensitivity % (95% CI)	Summary specificity % (95% CI)	Positive predictive value % (95% CI)*	Negative predictive value % (95% CI)*
Isoniazid	2 studies reporting on 6 study cohorts (1083)	756 (69.8)	94.2 (87.5 to 97.4)	98.5 (92.6 to 99.7)	76.9 (38.8 to 94.6)	99.7 (99.4 to 99.9)
Isoniazid	**1 study reporting on 4 study cohorts (605)**	**489 (80.8)**	**95.5 (85.2 to 98.7)**	**97.1 (82.4 to 99.6)**	**63.5 (19.5 to 92.6)**	**99.8 (99.2 to 99.9)**
Fluoro-quinolones	2 studies **reporting on** 6 study cohorts (1021)	381 (37.3)	93.2 (88.1 to 96.2)	98.0 (90.8 to 99.6)	70.6 (34 to 91.8)	99.7 (99.4 to 99.8)
Fluoro-quinolones	**1 study reporting on 4 study cohorts (604)**	**222 (36.8)**	**93.4 (84.3 to 97.4)**	**96.7 (85.3 to 99.3)**	**59.7 (23.8 to 87.5)**	**99.7 (99.2 to 99.9**)

Abbreviations: **CI:** confidence interval; **№**: number.
Results from the sensitivity analyses (**in bold**) in which the manufacturer sponsored study was excluded. The population is people irrespective of rifampicin resistance and the reference standard is phenotypic drug susceptibility testing.
Study cohorts were treated as distinct units in the meta-analyses.
*Prevalence of drug resistance for calculating predictive values was 5%.

APPENDICES

Appendix 1. Glossary of terms related to drug resistance testing

Amplification

Amplification is replication of a deoxyribonucleic acid (DNA) fragment to generate copies. Both the original and the newly synthesized copies can be described as the amplicons.

Bacteriologically confirmed

Refers to a biological specimen that is positive for tuberculosis by smear, culture, or Xpert MTB/RIF, Xpert MTB/RIF Ultra, Truenat MTB or another WHO-recommended rapid diagnostic test (see also **Microbiological reference standard**).

Codon

A codon is a sequence of three nucleotides (building blocks) in a DNA or ribonucleic acid (RNA) molecule that may encode, among other things, a specific amino acid.

Critical concentration

The critical concentration of a tuberculosis agent (drug) has been adopted and modified from international convention. The critical concentration is defined as the lowest concentration of a tuberculosis agent in vitro that will inhibit the growth of 99% of phenotypically wild type strains of *Mycobacterium tuberculosis (M tuberculosis)* complex.

Cultured isolate

Cultured isolate refers to *M tuberculosis* bacteria from a clinical specimen that have been grown. For tuberculosis diagnosis, a volume of the clinical specimen is processed and incubated under conditions that promote *M tuberculosis* growth. The bacteria that are grown are referred to a cultured isolate.

DNA sequencing

DNA sequencing is a process to determine the nucleotide (adenine (A), cytosine (C), guanine (G), and thymine (T)) sequence of fragments of DNA. By comparison of DNA sequences from distinct tuberculosis isolates, variations known as mutations can be identified. Some mutations in *M tuberculosis* are known to be associated with drug resistance.

Drug susceptibility testing

Drug susceptibility tests determine whether *M tuberculosis* bacteria are susceptible or resistant to drugs. Testing may be undertaken using phenotypic or genotypic analyses.

eis promoter

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to second-line injectable drugs, amikacin and kanamycin.

fabG1

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to isoniazid.

Genotypic drug susceptibility testing (gDST)

Genotypic drug susceptibility testing (gDST) involves detecting predetermined mutations in DNA that are known to make the bacteria resistant to a drug. When mutations causing drug resistance are unknown, gDST is not useful.

gDST can be targeted (limited to a certain number of loci for a drug) or genome-wide. Sanger sequencing, a targeted sequencing method, is limited in its depth (x1 vs. x100 for whole genome sequencing). Deep sequencing methods have greater resolution than the Sanger sequencing method. They also appear robust when performed on DNA extracted directly from a specimen (versus a cultured isolate), especially if that specimen is rich in mycobacteria. As with any method that is targeted, targeted gDST will miss phenotypic resistance causing mutations that occur outside of the target, simply because it is not designed to evaluate that region.

Genome-wide gDST typically refers to whole genome sequencing. Importantly, although whole genome sequencing could have been performed, some investigators might only use it in a manner equivalent to targeted sequencing of certain regions. For example, if whole genome sequencing coverage was poor in a region known to be important for resistance, but otherwise adequate in other regions important for resistance, whole genome sequencing will serve in this case as a limited form of targeted sequencing. In other words, even though most of the genome may be sequenced, we may not know where to look for resistance associated variants.

gyrA

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to fluoroquinolones.

gyrB

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to fluoroquinolones.

Heteroresistance

Heteroresistance is defined as resistance to certain drugs in a subset of a larger microbial population that is generally considered susceptible to these drugs according to traditional phenotypic drug susceptibility testing.

Indeterminate test result

An indeterminate Xpert MTB/XDR test result is one that indicates that resistance to a given drug could not definitively be detected based on the test's algorithm.

***inhA* promoter**

Gene target included in the Xpert MTB/XDR test to detect tuberculosis and resistance to isoniazid and ethionamide. Mutations in the *inhA* promoter region of tuberculosis are known to confer low-level resistance to isoniazid and high-level cross-resistance to ethionamide.

Intergenic region

Is a region of DNA sequence located between genes and a subset of non-coding DNA. Some intergenic regions act to control coding regions (genes) nearby.

katG

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to isoniazid.

Locus

A locus is the position of a genetic feature in the DNA sequence, like a genetic street address. Loci are standardized between genomes by reference to a common reference genome, such as H37Rv for *Mycobacterium tuberculosis*.

Microbiological reference standard

Refers to a biological specimen that is positive for tuberculosis by smear, culture, or a WHO-recommended rapid diagnostic test, such as Xpert MTB/RIF, Xpert MTB/RIF Ultra, Truenat MTB, or other WHO-recommended rapid diagnostic test (also see B**acteriologically confirmed**). Recently, the term 'microbiological reference standard' has come into use; particularly in WHO evaluations of new diagnostic tests.

Mutation

A mutation is a change in a DNA sequence. Mutations can result from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to chemicals called mutagens, or infection by viruses.

Non-determinate test result

A non-determinate Xpert MTB/XDR test result is one that results in an Error, Invalid, or No Result and can be due to an operator error, instrument, or cartridge issue.

***oxyR-ahpC* intergenic region**

Gene targets included in the Xpert MTB/XDR test to detect mutations that confer resistance to isoniazid.

Phenotypic drug susceptibility testing (pDST)

Phenotypic testing requires growth of *Mycobacterium tuberculosis* in the presence of drugs at a specific concentration that will inhibit the growth of susceptible bacteria or have no impact on growth of resistant bacteria.

Presumptive tuberculosis

Presumptive tuberculosis refers to a patient who presents with symptoms or signs suggestive of tuberculosis (WHO Definitions and Reporting 2020).

Promoter region

A promoter region is a sequence of DNA where the transcriptional machinery binds before transcribing the DNA into RNA that may then be translated into an amino acid sequence.

Reflex test

The term reflex test refers to a diagnostic approach in which an initial test meets predetermined criteria (e.g. outside of the normal range), and a second test is performed automatically, usually without a request from the health care worker. For example, a urinalysis may be followed by a culture (reflex test) if in the urine, the presence of nitrites is detected or the number of white blood cells is increased suggesting an infection. In the context of tuberculosis, culture may be used as a reflex test in a person living with HIV who has a Xpert MTB/RIF Ultra-negative result.

Resistance-determining region

A region of the *Mycobacterium tuberculosis* genome where mutations commonly cause resistance to a specific drug.

rrs

Gene target included in the Xpert MTB/XDR test to detect mutations that confer resistance to second-line injectable drugs, amikacin, kanamycin, and capreomycin.

Sanger sequencing

Technique for DNA sequencing based upon the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication, also known as 'the chain termination method'.

Targeted gene sequencing

The process for detecting predetermined mutations in DNA or genomic regions.

Whole genome sequencing (WGS)

The process of determining the complete genome sequence for a given organism (tuberculosis bacteria) at one time through next-generation sequencing methods. This method can determine the order of most nucleotides in a given genome and detect any variations relative to a reference genome using bioinformatics analyses.

Adapted from National Human Genome Research Institute 2022.

Appendix 2. Detailed search strategy

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations < 1946 to present

1 Extensively Drug-Resistant Tuberculosis/ or Tuberculosis, Multidrug-Resistant/ or Tuberculosis, Pulmonary/ or Mycobacterium Tuberculosis/

2 ((tuberculosis adj3 (lung or pulmonary)) or (tuberculosis adj3 respiratory)).mp.

3 (tuberculosis adj3 (drug resistan* or multidrug resistan* or mdr or xdr)).mp.

4 (((isoniazid adj3 resistance) or isoniazid) adj3 resistant).mp.

5 ((Ethionamide adj3 resistance) or (ethionamide adj3 resistant)).mp

6 ((Amikacin adj3 resistance) or (amikacin adj3 resistant)).mp.

7 ((Fluoroquinolone adj3 resistance) or (Fluoroquinolone adj3 resistant)).mp.

8 (Second-line injectable drug adj3 resistance).mp.

9 (Second-line injectable drug adj3 resistant).mp.

10 ((SLID adj3 resistance) or (SLID adj3 resistant)).mp.

11 (MDR-TB or XDR-TB).tw.

12 ((isoniazid or fluoroquinolone or "second-line injectable drug" or SLID) adj3 (monoresist* or mono-resist*)).tw.

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 (cartridge adj3 test*).mp.

15 cartridge*.ab. or cartridge*.ti.

16 (Molbio or Truenat or Cepheid or Xpert* or Bioneer or Hain).mp.

17 Genexpert*.mp.

18 exp Point-of-Care Systems/

19 (drug susceptibility test* or drug resistance test* or (rapid adj3 (detect* or test* or diagnos*)) or (poc or poct or "point of care")).mp.

20 14 or 15 or 16 or 17 or 18 or 19

21 13 and 20

22 Limit 21 to yrs “2015-Current”

Embase OVID

1 drug resistant tuberculosis/ or extensively drug resistant tuberculosis/ or multidrug resistant tuberculosis/ or lung tuberculosis/ or Mycobacterium Tuberculosis/

2 ((tuberculosis adj3 (lung or pulmonary)) or (tuberculosis adj3 respiratory)).mp.

3 (tuberculosis adj3 (drug resistan* or multidrug resistan* or mdr or xdr)).mp.

4 (((isoniazid adj3 resistance) or isoniazid) adj3 resistant).mp.

5 ((Ethionamide adj3 resistance) or (ethionamide adj3 resistant)).mp.

6 ((Amikacin adj3 resistance) or (amikacin adj3 resistant)).mp.

7 ((Fluoroquinolone adj3 resistance) or (Fluoroquinolone adj3 resistant)).mp.

8 (Second-line injectable drug adj3 resistance).mp.

9 (Second-line injectable drug adj3 resistant).mp.

10 ((SLID adj3 resistance) or (SLID adj3 resistant)).mp.

11 (MDR-TB or XDR-TB).tw.

12 ((isoniazid or fluoroquinolone or "second-line injectable drug" or SLID) adj3 (monoresist* or mono-resist*)).tw.

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 (cartridge adj3 test*).mp.

15 cartridge*.ab. or cartridge*.ti.

16 (Molbio or Truenat or Cepheid or Xpert* or Bioneer or Hain).mp.

17 Genexpert*.mp.

18 exp Point-of-Care Systems/

19 (drug susceptibility test* or drug resistance test* or (rapid adj3 (detect* or test* or diagnos*)) or (poc or poct or "point of care")).mp.

20 14 or 15 or 16 or 17 or 18 or 19

21 13 and 20

22 Limit 21 to yrs “2015-Current”

CPCI-S, SCI-EXPANDED, Biosis (Web of Science)

#4 (#1) AND #2 and 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 (Publication Years)

#3 (#1) AND #2

#2 (cartridge test*) or (Molbio or Truenat or Cepheid or Xpert* or Bioneer or Hain) or Genexpert* or Point-of-Care System* (Topic)

#1 (tuberculosis AND (drug resistan* or multidrug resistan* or mdr or xdr)) (Topic) or tuberculosis AND (isoniazid resist* or Ethionamide resist* or Amikacin resist* or Fluoroquinolone resist* or Second-line injectable drug resist*) (Topic)

Scopus

(TITLE-ABS-KEY ((cartridge AND test*) OR (molbio OR truenat OR cepheid OR xpert* OR bioneer OR hain) OR genexpert* OR point-of-care AND system*)) AND ((TITLE-ABS-KEY (tuberculosis AND (drug AND resistan* OR multidrug AND resistan* OR mdr OR xdr))) OR (TITLE-ABS-KEY (tuberculosis AND ((isoniazid AND resist*) OR (ethionamide AND resist*) OR (amikacin AND resist*) OR (fluoroquinolone AND resist*) OR (second-line AND injectable AND drug AND resist*))))) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR, 2015))

Database: LILACS

Search on: (tuberculosis AND (drug resistan$ or multidrug resistan$ or mdr or xdr)) [Words] and (cartridge test$) or (Molbio or Truenat or Cepheid or Xpert$ or Bioneer or Hain) or Genexpert$ or Point-of-Care System$ [Words] and 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 [Country, year publication]

Clinicaltrials.gov, WHO ICTRP, ISRCTN

Xpert, Genexpert and Tuberculosis, Multidrug-Resistant ; Multi-Drug Resistant Tuberculosis; MDR Tuberculosis; MDR-TB; Multidrug-Resistant TB

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ab(tuberculosis) AND ab(Xpert or genexpert or cartridge) limit to 2015-01-01 - 2021-09-16

Appendix 3. Data extraction form

Study	
Name of data extractor	1 – SP 2 – KRS 3 – other, specify GT, MdV, GD
First author	
Corresponding author and email	
Was author contacted?	1 – yes 2 – no If yes, dates(s)
Title of paper	
Year (of publication)	
Year (study start date)	
Language	1 – English 2 – other If other, specify:
Was the study conducted without industry sponsorship?	1 – yes 2 – no 9 – unknown/not reported

(Continued)

If industry sponsorship was present, select one item from the list	Answers ordered from least to most industry involvement 1 – donation of test for use in study 2 – test at a special preferred price 3 – receipt of educational support, grants, or speaking fees 4 – financial relationship – author is employee/consultant/stockholder 5 – involvement in design, analysis, or manuscript production
Study addresses question A (detection of isoniazid only), B (detection of second-line only), (detection of both isoniazid and second-line) C	1 – A 2 – B 3 – C Circle as many options as required
What was the aim of this study in authors' own words?	
Country of laboratory where test was run	
World Bank Classification of laboratory country	1 – low 2 – middle 3 – high 8 – other
Laboratory setting; describe as written in the paper	1 – primary care laboratory 2 – intermediate-level laboratory 3 – central-level laboratory 8 – other, specify 9 – unknown/not reported
Study design	1 – cross-sectional 2 – cohort 3 – single gate diagnostic study 8 – other, specify 9 – unknown/not reported
Participant selection	1 – consecutive 2 – random 3 – convenience 8 – other, specify 9 – unknown/not reported

(Continued)

Comments about study design		
Number after screening by exclusion and inclusion criteria		9 – unknown/not reported
Number included in analysis (# screened – # exclusions)		9 – unknown/not reported
Did the study include specimens and/or cultured isolates for testing?		1 – specimens 2 – isolates 3 – both 9 – unknown/not reported
Characteristics of participants		
Age	mean SD median IQR range 9 – unknown/not reported	
Gender	male female total # females/total (%) 9 – unknown/not reported	
HIV status	positive negative unknown total # HIV positive/total (%) 9 – unknown/not reported	
Previous tuberculosis treatment	yes no unknown total # previous tuberculosis/total (%) = 9 – unknown/not reported	
Type of partici-pants/specimens tested	1 – presumptive tuberculosis 2 – irrespective of rifampicin resistance 3 – with known (detected) rifampicin resistance	

(Continued)

	8 – other, specify: 9 – unknown/not reported
Reference standards 1 – pDST 2 – gDST 3 – composite The composite reference standard is pDST and gDST, where at least one component test is positive.	
Isoniazid	1 – pDST (specify type and critical concentrations) 2 – sequencing of the *katG, inhA promoter,* and *fabG1* gene 3 – both 1 and 2 in all specimens (specify culture information in 1) 9 -unknown/not reported 1a – MGIT, LJ, other 1b – isoniazid critical concentration MGIT – 0.1 WHO concentration LJ – 0.2 WHO concentration
Fluoroquinolones	1 – pDST (specify type and critical concentrations) 2 – sequencing of the *gyrA* and *gyrB* gene 3 – both 1 and 2 in all specimens (specify culture info in 1) 9 – unknown/not reported 1a – MGIT, LJ, other 1b – drugs used for this class and critical concentration Levofloxacin MGIT – 1.0 WHO concentration LJ – 2.0 WHO concentration Moxifloxacin (critical concentration) MGIT – 0.25 WHO concentration LJ – 1.0 WHO concentration Moxifloxacin (clinical breakpoint) 7H10 – 2.0 WHO concentration MGIT – 1.0 WHO concentration
Ethionamide	1 – pDST (specify type and critical concentrations) 2 – sequencing of the *inhA promoter* gene 3 – both 1 and 2 in all specimens (specify culture information in 1)

(Continued)

	9 – unknown/not reported 1a – MGIT, LJ, other 1b – ethionamide critical concentration MGIT – 5.0 WHO concentration LJ – 40.0 WHO concentration	
Amikacin	1 – pDST (specify type and critical concentrations) 2 – sequencing of the *rrs* gene 3 – both 1 and 2 in all specimens (specify culture info in 1) 9 – unknown/not reported 1a – MGIT, LJ, other 1b – amikacin critical concentration MGIT – 1.0 WHO concentration LJ – 30.0 WHO concentration	
Test information		
Was microscopy used?	1 – yes 2 – no 9 – unknown/not reported	
Smear status of specimens (if applicable)	positive negative unknown total	
Specimen information		
Type of specimen (may include expectorated sputum) if test performed directly on a specimen		1 – all expectorated 2 – all induced 3 – both types 8 – other 9 – unknown/not reported describe
Were results for Xpert MTB/XDR and culture obtained using the same specimen?		1 – yes 2 – no 3 – not applicable 9 – unknown/not reported

(Continued)

Pretreatment processing procedure if performed for Xpert MTB/XDR specimen	1 – none 2 – NALC-NaOH 3 – NaOH (Petroff) 8 – other 9 – unknown/not reported
For Xpert MTB/XDR specimen, what was the condition of the specimen when tested?	1 – fresh 2 – frozen 3 – both 9 – unknown/not reported
If fresh, specify:	1 – tested after storage at room temperature or refrigerated within 48 hours of collection 2 – tested after storage at room temperature or refrigerated > 48 hours after collection 9 – unknown/not reported
If frozen, specify:	1 – tested after frozen < 1 year of storage 2 – tested frozen ≥ 1 year storage 9 – unknown/not reported
Proportion contaminated cultures, if provided:	= # of contaminated cultures total # cultures performed 9 – unknown/not reported
Proportion inconclusive sequencing results, if provided (does not apply to discrepant analysis)	= # of inconclusive sequencing total # sequencing performed 9 – unknown/not reported
Were patient-important outcomes evaluated?	1 – yes 2 – no 9 – unknown/not reported
Time to diagnosis and Time to report	Isoniazid Fluoroquinolone Ethionamide Amikacin 9 – unknown (45 days (27–122 days) for liquid culture)
Time to treatment initiation	Isoniazid

(Continued)

Fluoroquinolone

Ethionamide

Amikacin

9 – unknown

Tables

Tuberculosis detection

Tuberculosis detection, all		Culture		
		Yes	No	Total
Xpert MTB/XDR Result	Positive			
	Negative			
	Total			

Isoniazid resistance detection, direct testing, in people irrespective of rifampicin resistance

Isoniazid, all		pDST		
		Yes	No	Total
Xpert MTB/XDR Result	Positive			
	Negative			
	Total			

Isoniazid, smear positive		pDST		
		Yes	No	Total
Xpert MTB/XDR Result	Positive			
	Negative			
	Total			

Isoniazid, smear negative		pDST		
		Yes	No	Total
Xpert MTB/XDR Result	Positive			
	Negative			
	Total			

Add tables as needed.

Abbreviations: **gDST:** genotypic drug susceptibility testing; **IQR:** interquartile range; **LJ:** Löwenstein Jensen; **MGIT:** Mycobacteria Growth Indicator Tube; **pDST**: phenotypic drug susceptibility testing; **SD**: standard deviation; **WHO:** World Health Organization.

Appendix 4. QUADAS-2 tailored to the review

Domain 1: patient selection

Detection of pulmonary tuberculosis

Risk of bias: could the selection of patients have introduced bias?

Signalling question 1: was a consecutive or random sample of patients enrolled?

We answered yes if the study enrolled a consecutive or random sample of eligible participants; no if the study selected participants by convenience; and unclear if the study did not report the manner of participant selection or we could not determine this.

Signalling question 2: was a case-control design avoided?

We answered yes for all studies.

Signalling question 3: did the study avoid inappropriate exclusions?

We answered yes if the study included both smear-positive and smear-negative participants; no if the study included primarily or exclusively smear-positive or smear-negative participants; and unclear if we could not determine this. If, at the time of specimen collection, participants were receiving tuberculosis treatment, we answered no because treatment reduces the culturability of *M tuberculosis* quicker than it reduces the amount of MTB DNA. Treatment therefore confounds the relationship between Xpert MTB/XDR-positivity and culture-positivity (the reference standard), potentially leading to underestimation of specificity. We also judged high-risk of bias if we thought most participants were enrolled based on known rifampicin resistance.

Applicability: are there concerns that the included participants and setting do not match the review question?

We considered low concern if the included patients matched the review question; high concern if the included patients did not match the review question; and unclear concern if we could not determine. Our assessment included consideration of prior testing and the clinical setting. We answered low concern if participants were people with presumed pulmonary tuberculosis; high concern if participants received prior testing and were included based on a positive Xpert MTB/RIF or Xpert MTB/RIF Ultra result; and unclear concern if participants received prior testing but we could not tell if inclusion was based on a positive Xpert MTB/RIF or Xpert MTB/RIF Ultra result. We answered low concern if participants were evaluated as outpatients (with either expectorated or induced sputum) in local hospitals or primary care centres. We answered high concern if participants were evaluated exclusively as inpatients in tertiary care centres. We answered unclear concern if the clinical setting was not reported or there was insufficient information to make a decision. We also answered unclear concern if testing was performed at a central-level laboratory and the clinical setting was not reported or if, for example, it was difficult to determine whether the laboratory provided services mainly to very sick people or people with a broader clinical spectrum of illness. We also answered high concern if patients were on treatment or their treatment status was unclear, as such patients have already been diagnosed with tuberculosis.

Detection of drug resistance

Risk of bias: could the selection of participants have introduced bias?

Signalling question 1: was a consecutive or random sample of participants enrolled?

We answered the same as for detection of tuberculosis.

Signalling question 2: was a case-control design avoided?

We answered yes if the study enrolled people with tuberculosis with suspected or sufficiently high pretest probability (per World Health Organization guidelines) for resistance to isoniazid, second-line drugs, or both isoniazid and second-line drugs; no if the study enrolled people with tuberculosis with confirmed previously known resistance to the drug in question; and unclear for all other scenarios or if it was not clearly reported. We considered that accuracy studies may have a cross-sectional design even when the reference standard is performed before the index test if both cases and controls are sampled from a single source population.

Signalling question 3: did the study avoid inappropriate exclusions?

We answered yes for people who were previously treated for tuberculosis. We answered no if people who were previously treated were excluded. People previously tested for tuberculosis have a higher risk of having drug resistance and are likely to be the target population for initial use of Xpert MTB/XDR. If people with samples known to be heteroresistant (a mix of susceptible and resistant tuberculosis strains in the specimen) were excluded, which is particularly relevant for the fluoroquinolones, we answered answer no. We answered unclear if we could not determine this.

Applicability: are there concerns that the included participants and setting do not match the review question?

We answered low concern if the selected clinical specimens or isolates matched the review question, which reflects the way the test will be used in practice. We answered high concern if the selected specimens or isolates did not represent those for whom the test will be used in practice, such as in people who do not require investigation for resistance to the drugs in question. We answered unclear concern if we could not determine this.

Domain 2: index test

Detection of pulmonary tuberculosis

Risk of bias: could the conduct or interpretation of the index test have introduced bias?

Signalling question 1: were the index test results interpreted without knowledge of the results of the reference standard?

We answered yes for all studies since Xpert MTB/XDR results are automatically generated and the user is provided with printable test results, thus, avoiding subjective interpretation.

Signalling question 2: if a threshold was used, was it pre-specified?

We answered yes for all studies.

Applicability: are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Variations in test technology, execution, or interpretation may affect estimates of the diagnostic accuracy of a test. We judged the study of low concern for applicability if the test was performed as recommended by the manufacturer. We judged the study of high concern if the test was applied differently than recommended by the manufacturer, for example, if the test was applied to summary sputa. We judged the study of unclear concern if we could not determine this.

Detection of drug resistance

Risk of bias: could the conduct or interpretation of the index test have introduced bias?

Signalling question 1: were the index test results interpreted without knowledge of the results of the reference standard?

We answered yes for all studies since Xpert MTB/XDR results are automatically generated and the user is provided with printable test results, thus, avoiding subjective interpretation.

Signalling question 2: if a threshold was used, was it pre-specified?

We answered yes for all studies.

Applicability: are there concerns that the index test, its conduct, or its interpretation differ from the review question?

We recorded the same judgements as for detection of pulmonary tuberculosis.

Domain 3: reference standard

Detection of pulmonary tuberculosis

Risk of bias: could the reference standard, its conduct, or its interpretation have introduced bias?

Signalling question 1: is the reference standard likely to correctly classify the target condition?

We answered yes for all studies because a microbiological reference standard for *M tuberculosis* is a criterion for inclusion in the review.

Signalling question 2: were the reference standard results interpreted without knowledge of the results of the index test?

We answered yes if the reference test provided an automated result (e.g. MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory or performed by different people (or both). We answered no if the study stated that the reference standard result was interpreted with knowledge of the Xpert MTB/XDR test result. We answered unclear if we could not determine this.

Applicability: are there concerns that the target condition as defined by the reference standard does not match the question?

We answered high concern if a type of culture was not used as part of the reference standard, because studies that include only DNA-based tests do not directly measure live *M tuberculosis*. We answered low concern if culture was performed. We answered unclear concern if we could not determine this.

Detection of drug resistance

Risk of bias: could the reference standard, its conduct, or its interpretation have introduced bias?

We considered the reliability of the different reference standards for the different drugs (Heyckendorf 2018).

Signalling question 1.1: Is the reference standard likely to correctly classify the target condition, pDST?

Signalling question 1.2: Is the reference standard likely to correctly classify the target condition, gDST?

Signalling question 1.3: Is the reference standard likely to correctly classify the target condition, composite?

We answered these questions as follows.

Drug	pDST*	gDST using targeted sequencing	Composite (pDST* and gDST using targeted sequencing)	gDST using whole genome sequencing	Composite (pDST* and gDST using whole genome sequencing)
Isoniazid	Yes	Unclear if few loci were investigated, and yes, if all relevant loci were analysed Loci required for yes: *katG*, *inhA* promoter, *oxyR-ahpC* intergenic region, and *fabG1*	Yes	Unclear if few loci were investigated, and yes, if all relevant loci were analysed Loci required for yes: *katG*, *inhA* promoter, *oxyR-ahpC* intergenic region, and *fabG1*	Yes
Fluoroquinolones	Yes, will depend on critical concentration used for moxifloxacin	Yes Loci required for yes: *gyrA* and *gyrB*	Yes	Yes Loci required for yes: *gyrA* and *gyrB*	Yes
Ethionamide	No, there is considerable overlap in the MICs of *M tuberculosis* isolates with and without resistance-causing variants. This means there is	Unclear if few loci were investigated, and yes, if all relevant loci were analysed Loci required for yes: *ethA*, *ethR,* and *inhA* promoter	Unclear	Unclear if few loci were investigated, and yes, if all relevant loci were analysed Loci required for yes: *ethA*, *ethR,* and *inhA* promoter No if only the *inhA* promoter was analysed	Unclear

(Continued)

	considerable overlap in the distribution of MICs for resistant and wild-type isolates	No if only the *inhA* promoter was analysed			
Amikacin	Yes	Yes, if all relevant loci were analysed Loci required for yes: *rrs* and *eis* promoter	Yes	Yes, if all relevant loci were analysed Loci required for yes: *rrs* and *eis* promoter	Yes

Abbreviations: **gDST**: genotypic drug susceptibility testing; **MIC**: minimum inhibitory concentration; **pDST**: phenotypic drug susceptibility testing.
*We used the currently recommended World Health Organization critical concentrations as a benchmark for judging risk of bias (Appendix 11). For *M tuberculosis*, the antimicrobial susceptibility testing critical concentration is defined as the lowest concentration of an anti-tuberculosis agent in vitro that will inhibit the growth of 99% of phenotypically wild type strains of *Mtuberculosis* complex (WHO Critical Concentrations 2018; WHO Critical Concentrations 2021).

We added the following signalling questions.

Signalling question 2.1: Were the reference standard results interpreted without knowledge of the results of the index tests, pDST?

Signalling question 2.2: Were the reference standard results interpreted without knowledge of the results of the index tests, gDST?

Signalling question 2.3: Were the reference standard results interpreted without knowledge of the results of the index tests, composite?

For pDST, we answered yes if the reference test provided an automated result (e.g. if liquid culture was used as in MGIT 960 DST), blinding was explicitly stated, or it was clear that the reference test was performed at a separate laboratory, or performed by different people, or both. Of note, pDST on solid media is not automated. We answered no if the study stated that the reference standard result was interpreted with knowledge of the Xpert MTB/XDR test result. We answered unclear if we could not determine this. For gDST, we answered yes for all studies since the results for the reference standard are automated.

We added the following signalling question.

Signalling question 3: Were the index test and reference standard performed using the same material (clinical specimen or sediment, or cultured isolate)?

Phenotypic DST (pDST) and genotypic DST (gDST) for reference standard testing can be performed on an isolate that has undergone (potentially multiple rounds) of culture in drug-free media. This may lead to the depletion of resistant strains present in the original specimen (which would have been used for the Xpert MTB/XDR testing if direct testing was performed) and cause discrepant results. We think this is an important question as it addresses heteroresistance, which often explains discordance between genotypic and phenotypic results.

For direct testing of a clinical specimen by Xpert MTB/XDR: we answered yes if the reference test was performed directly on the same clinical specimen; no if the reference standard was performed on a culture isolate; and unclear if we could not determine this. For indirect testing of a culture isolate by Xpert MTB/XDR: we answered yes if the reference test was performed on the same culture isolate (e.g. indirect sequencing); no if the reference standard was performed on a different culture isolate, or specimen; and unclear if we could not determine this.

Applicability: are there concerns that the target condition as defined by the reference standard does not match the question?

We judged applicability of low concern for all studies because specimens to be subsequently tested for drug resistance will have already been identified as *M tuberculosis* complex positive.

Domain 4: flow and timing

Detection of tuberculosis

Risk of bias: could the patient flow have introduced bias?

Signalling question 1: was there an appropriate interval between the index test and reference standard?

In most studies, we expected the reference standard to be performed at the same time as Xpert MTB/XDR. However, in some studies, the reference standard may have been performed on a different sample collected at an earlier time. This case applies to some cultured isolates, whose drug susceptibility profile might have been confirmed before Xpert MTB/XDR was available. We answered yes if Xpert MTB/XDR and the reference standard were performed at the same time or were separated by less than 14 days. We answered no if Xpert MTB/XDR and the reference standard were not performed at the same time and were separated by 14 days or more. As people suspected of second-line drug resistance are often receiving treatment for tuberculosis, it is possible that variation in the microbial population of specimens collected at different time points may occur. We answered unclear if we could not determine this.

Signalling question 2: did all patients receive the same reference standard?

We answered yes if the reference standard was applied to all participants or a random sample of participants, no if the reference standard was only applied to a selective group of participants, and unclear if it was not stated in the paper or if the authors failed to answer this question.

Signalling question 3: were all patients included in the analysis?

We determined the answer to this question by comparing the number of participants enrolled with the number of participants included in the 2×2 tables. We noted if the study authors reported the number of inconclusive test results. We answered yes if the number of participants enrolled was clearly stated and corresponded to the number presented in the analysis or if exclusions were adequately described. We answered no if there were participants missing or excluded from the analysis and there was no explanation given. We answered unclear if insufficient information was given to assess whether participants were excluded from the analysis.

Detection of drug resistance

We answered the same as for detection of pulmonary tuberculosis.

Judgements for risk of bias assessments for a given domain.

- If we answered all signalling questions for a domain yes, then we judged risk of bias as low.
- If we answered all or most signalling questions for a domain no, then we judged risk of bias as high.
- If we answered only one signalling question for a domain no, we discussed further the risk of bias judgement.
- If we answered all or most signalling questions for a domain unclear, then we judged risk of bias as unclear.
- If we answered only one signalling question for a domain unclear, we discussed further the risk of bias judgement for the domain.

Appendix 5. Xpert MTB/XDR inconclusive results and missed cases

We used the following approach to describe the different types of inconclusive results.

Xpert MTB/XDR NON-DETERMINATE: Among specimens initially tested, we determined the proportion of Xpert MTB/XDR NON-DETERMINATE results and, of these, the number of ERROR, INVALID, and NO RESULT results. We also determined the percentage of non-determinate results remaining following retesting.

Xpert MTB/XDR INDETERMINATE: Among specimens reporting Xpert MTB/XDR MTB DETECTED, we determined the proportion that were Xpert MTB/XDR INDETERMINATE (drug resistance is only evaluated when tuberculosis is detected). Among specimens with results reported as Xpert MTB/XDR INDETERMINATE, we further determined the percentage that were resistant or susceptible by the reference standard.

Xpert MTB/XDR MTB NOT DETECTED: Among specimens with pDST results available, we determined the percentage that were Xpert MTB/XDR MTB NOT DETECTED. Among specimens with results reported as Xpert MTB/XDR MTB NOT DETECTED, we further determined the percentage that were resistant or susceptible according to pDST.

Xpert MTB/XDR NON-DETERMINATE results

The summary proportion of Xpert MTB/XDR non-determinate results was estimated to be 2.90% (95% CI: 1.97% to 3.84%).

In Omar 2020, upon initial Xpert MTB/XDR testing, of 531 specimens tested, 15 resulted in non-determinate results. There were 10 Error results, one Invalid result, and four No Result results. Therefore, the proportion of non-determinate results upon initial testing was 2.8%. The 15 specimens were retested, and 14 gave valid results. Only one of the 15 retested specimens resulted in an Error following its repeat test. Therefore, the proportion of non-determinate results following retesting was 0.2% (1/531).

In Penn-Nicholson 2021, upon initial Xpert MTB/XDR testing, of 709 specimens tested, 21 resulted in non-determinate results. Therefore, the proportion of non-determinate results upon initial testing was 3.0% (21/709). The 21 specimens were retested, and 19 gave valid results. Therefore, the proportion of non-determinate results following retesting was 0.3% (2/709).

One study reported Xpert MTB/XDR non-determinate results by smear status (Penn-Nicholson 2021). In this study, the proportion of Xpert MTB/XDR non-determinate results was 4.2% (9/216) in smear-negative specimens and 2.4% (12/491) in smear-positive specimens.

The phenotypic status of non-determinate results was not discernable for either study.

Xpert MTB/XDR INDETERMINATE results

Isoniazid resistance

Of 530 specimens tested, 498 specimens had an Xpert MTB/XDR MTB DETECTED result. Of these 498 specimens, two (0.4%) had indeterminate results for detection of resistance. By the pDST reference standard, of these two specimens, two (100%) were resistant and zero (0%) were susceptible (Omar 2020).

Of 709 specimens tested, 657 had an Xpert MTB/XDR MTB DETECTED result. Of these 657 specimens, two (0.3%) had indeterminate results for detection of resistance. None were indeterminate upon retesting (Penn-Nicholson 2021).

Fluoroquinolone resistance

Of 530 specimens tested, 498 specimens had an Xpert MTB/XDR MTB DETECTED result. Of these 498 specimens, four (0.8%) had indeterminate results for detection of resistance. By the pDST reference standard, of these four specimens, zero (0%) were resistant and four (100%) were susceptible (Omar 2020).

Of 709 specimens tested, 657 had an Xpert MTB/XDR MTB DETECTED result. Of these 657 specimens, nine (1.4%) had indeterminate results for detection of resistance. None were indeterminate upon retesting (Penn-Nicholson 2021).

Ethionamide resistance

Of 530 specimens tested, 498 specimens had an Xpert MTB/XDR MTB DETECTED result. Of these 498 specimens, none (0%) had an indeterminate result for detection of resistance (Omar 2020).

Of 709 specimens tested, 657 had an Xpert MTB/XDR MTB Detected result. Of these 657 specimens, one (0.2%) had an indeterminate result for detection of resistance. This specimen was no longer indeterminate upon retesting (Penn-Nicholson 2021).

Amikacin resistance

Of 530 specimens tested, 498 specimens had an Xpert MTB/XDR MTB DETECTED result. Of these 498 specimens, eight (1.6%) had indeterminate results for detection of resistance. By the pDST reference standard, of these eight specimens, zero (0%) were resistant and eight (100%) were susceptible (Omar 2020).

Of 709 specimens tested, 657 had an Xpert MTB/XDR MTB DETECTED result. Of these 657 specimens, 23 (3.5%) had indeterminate results for detection of resistance. One was indeterminate upon retesting (Penn-Nicholson 2021).

In Penn-Nicholson 2021, among specimens with results reported as Xpert MTB/XDR INDETERMINATE, we could not determine the proportion that were resistant or susceptible by the pDST reference standard.

Xpert MTB/XDR MTB NOT DETECTED

One study reported information about when Xpert MTB/XDR did not detect tuberculosis to begin with (missed cases) (Omar 2020).

Table. Summary of Xpert MTB/XDR MTB NOT DETECTED results by drug and drug susceptibility status

Drug	**Total pDST results**	**No. (%) Xpert MTB/XDR MTB NOT DETECTED**	**№** (%) resistant	**№** (%) susceptible
Isoniazid	512	32 (6.3%)	2 (6.3%)	30 (93.8%)
Fluoroquinolones	453	32 (7.1%)	1 (3.1%)	31 (96.9%)
Ethionamide	260	30 (11.5%)	2 (6.7%)	28 (93.3%)
Amikacin	445	32 (7.2%)	0 (0.0%)	32 (100.0%)

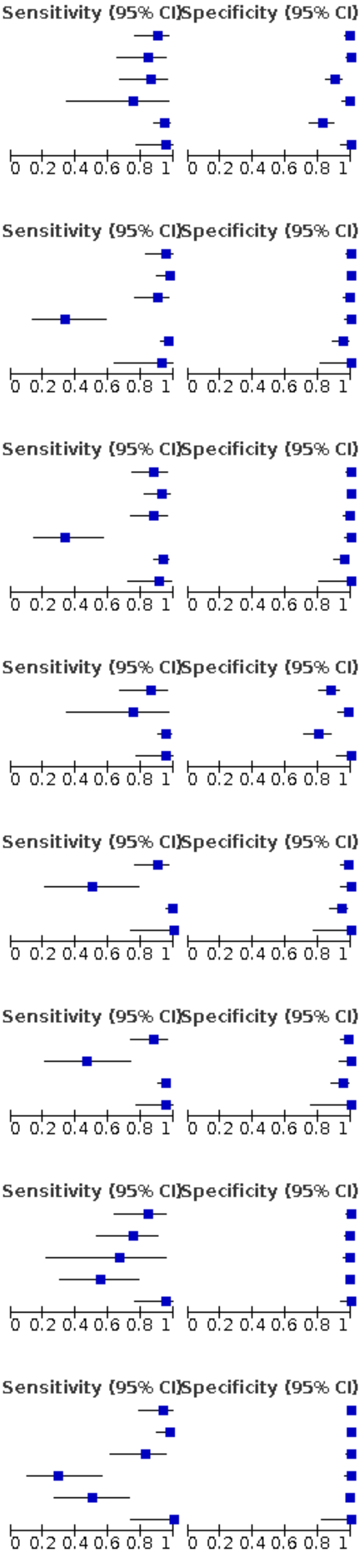
Abbreviaitons: **№**: number; **pDST:** phenotypic drug susceptibility testing.

Appendix 6. Xpert MTB/XDR for detection of resistance to kanamycin and capreomycin

Figure 12

Figure 12. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for resistance to kanamycin and capreomycin by population and reference standard. Study in the forest plots refers to a study cohort within

a multicentre study. pDST = phenotypic drug resistance testing; TP = true positive; FP = false positive; FN = false negative; TN = true negative.



Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	36	1	4	136	0.90 [0.76, 0.97]	0.99 [0.96, 1.00]
Omar 2020 South Africa	22	0	4	140	0.85 [0.65, 0.96]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	24	14	4	135	0.86 [0.67, 0.96]	0.91 [0.85, 0.95]
Penn-Nicholson 2021 India (New Delhi)	6	1	2	107	0.75 [0.35, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	111	19	7	93	0.94 [0.88, 0.98]	0.83 [0.75, 0.89]
Penn-Nicholson 2021 South Africa	21	0	1	59	0.95 [0.77, 1.00]	1.00 [0.94, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	37	0	2	138	0.95 [0.83, 0.99]	1.00 [0.97, 1.00]
Omar 2020 South Africa	51	0	1	234	0.98 [0.90, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	36	1	4	120	0.90 [0.76, 0.97]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	12	91	0.33 [0.13, 0.59]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	123	5	4	94	0.97 [0.92, 0.99]	0.95 [0.89, 0.98]
Penn-Nicholson 2021 South Africa	12	0	1	18	0.92 [0.64, 1.00]	1.00 [0.81, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, kanamycin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	37	0	5	141	0.88 [0.74, 0.96]	1.00 [0.97, 1.00]
Omar 2020 South Africa	51	0	4	231	0.93 [0.82, 0.98]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	36	1	5	119	0.88 [0.74, 0.96]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	14	89	0.33 [0.15, 0.57]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	126	4	9	89	0.93 [0.88, 0.97]	0.96 [0.89, 0.99]
Penn-Nicholson 2021 South Africa	21	0	2	17	0.91 [0.72, 0.99]	1.00 [0.80, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	24	14	4	102	0.86 [0.67, 0.96]	0.88 [0.81, 0.93]
Penn-Nicholson 2021 India (New Delhi)	6	1	2	65	0.75 [0.35, 0.97]	0.98 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	109	19	5	79	0.96 [0.90, 0.99]	0.81 [0.71, 0.88]
Penn-Nicholson 2021 South Africa	21	0	1	39	0.95 [0.77, 1.00]	1.00 [0.91, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	36	1	4	91	0.90 [0.76, 0.97]	0.99 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	6	0	6	54	0.50 [0.21, 0.79]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	121	5	1	82	0.99 [0.96, 1.00]	0.94 [0.87, 0.98]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]

Xpert MTB/XDR, direct, with known rifampicin resistance, kanamycin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	36	1	5	90	0.88 [0.74, 0.96]	0.99 [0.94, 1.00]
Penn-Nicholson 2021 India (New Delhi)	7	0	8	53	0.47 [0.21, 0.73]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	124	4	6	77	0.95 [0.90, 0.98]	0.95 [0.88, 0.99]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	21	0	4	142	0.84 [0.64, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (Mumbai)	18	1	6	153	0.75 [0.53, 0.90]	0.99 [0.96, 1.00]
Penn-Nicholson 2021 India (New Delhi)	4	1	2	109	0.67 [0.22, 0.96]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 Moldova	10	1	8	211	0.56 [0.31, 0.78]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	20	0	1	59	0.95 [0.76, 1.00]	1.00 [0.94, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, gDST

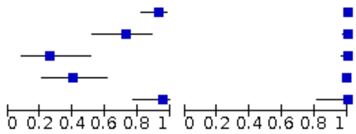
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 China	29	0	2	146	0.94 [0.79, 0.99]	1.00 [0.98, 1.00]
Omar 2020 South Africa	49	0	1	236	0.98 [0.89, 1.00]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	0	4	139	0.83 [0.61, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	12	92	0.29 [0.10, 0.56]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	10	1	10	205	0.50 [0.27, 0.73]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	19	1.00 [0.74, 1.00]	1.00 [0.82, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, composite

Figure 12. (Continued)

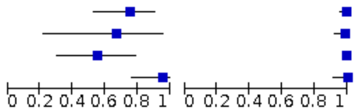
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, capreomycin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Omar 2020 South Africa	49	0	4	233	0.92 [0.82, 0.98]	1.00 [0.98, 1.00]
Penn-Nicholson 2021 India (Mumbai)	19	0	7	136	0.73 [0.52, 0.88]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	14	90	0.26 [0.09, 0.51]	1.00 [0.96, 1.00]
Penn-Nicholson 2021 Moldova	10	1	15	200	0.40 [0.21, 0.61]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	18	0.95 [0.77, 1.00]	1.00 [0.81, 1.00]



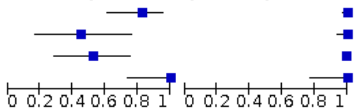
Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, pDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	18	1	6	120	0.75 [0.53, 0.90]	0.99 [0.95, 1.00]
Penn-Nicholson 2021 India (New Delhi)	4	1	2	67	0.67 [0.22, 0.96]	0.99 [0.92, 1.00]
Penn-Nicholson 2021 Moldova	10	1	8	193	0.56 [0.31, 0.78]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	20	0	1	39	0.95 [0.76, 1.00]	1.00 [0.91, 1.00]



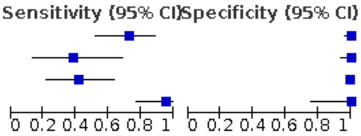
Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, gDST

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	0	4	110	0.83 [0.61, 0.95]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	6	55	0.45 [0.17, 0.77]	1.00 [0.94, 1.00]
Penn-Nicholson 2021 Moldova	10	1	9	189	0.53 [0.29, 0.76]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	12	0	0	14	1.00 [0.74, 1.00]	1.00 [0.77, 1.00]



Xpert MTB/XDR, direct, with known rifampicin resistance, capreomycin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021 India (Mumbai)	19	0	7	107	0.73 [0.52, 0.88]	1.00 [0.97, 1.00]
Penn-Nicholson 2021 India (New Delhi)	5	0	8	54	0.38 [0.14, 0.68]	1.00 [0.93, 1.00]
Penn-Nicholson 2021 Moldova	10	1	14	184	0.42 [0.22, 0.63]	0.99 [0.97, 1.00]
Penn-Nicholson 2021 South Africa	21	0	1	13	0.95 [0.77, 1.00]	1.00 [0.75, 1.00]



Appendix 7. Xpert MTB/XDR for detection of drug resistance, direct versus indirect testing

Figure 13

Figure 13. Forest plots of Xpert MTB/XDR sensitivity and specificity for resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin, testing on sputum (direct testing) versus testing on cultured isolates (indirect testing), composite reference standard. Data were reported for all study cohorts combined. TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Xpert MTB/XDR, direct, isoniazid, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	459	0	28	77	0.94 [0.92, 0.96]	1.00 [0.95, 1.00]

Xpert MTB/XDR, indirect, isoniazid, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	461	0	26	77	0.95 [0.92, 0.96]	1.00 [0.95, 1.00]

Xpert MTB/XDR, direct, fluoroquinolone, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	222	2	12	294	0.95 [0.91, 0.97]	0.99 [0.98, 1.00]

Xpert MTB/XDR, indirect, fluoroquinolone, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	224	0	10	296	0.96 [0.92, 0.98]	1.00 [0.99, 1.00]

Xpert MTB/XDR, direct, ethionamide, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	178	1	150	212	0.54 [0.49, 0.60]	1.00 [0.97, 1.00]

Xpert MTB/XDR, indirect, ethionamide, composite, direct comparison

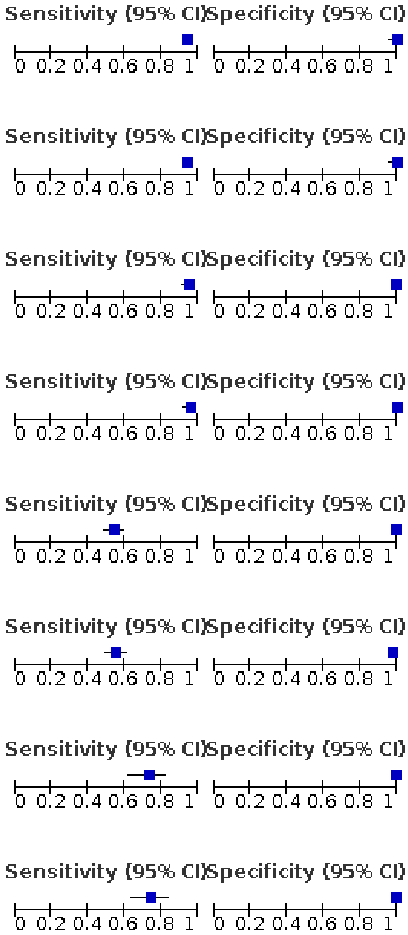
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	182	4	146	209	0.55 [0.50, 0.61]	0.98 [0.95, 0.99]

Xpert MTB/XDR, direct, amikacin, composite, direct comparison

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	60	2	22	425	0.73 [0.62, 0.82]	1.00 [0.98, 1.00]

Xpert MTB/XDR, indirect, amikacin, composite, direct comparison

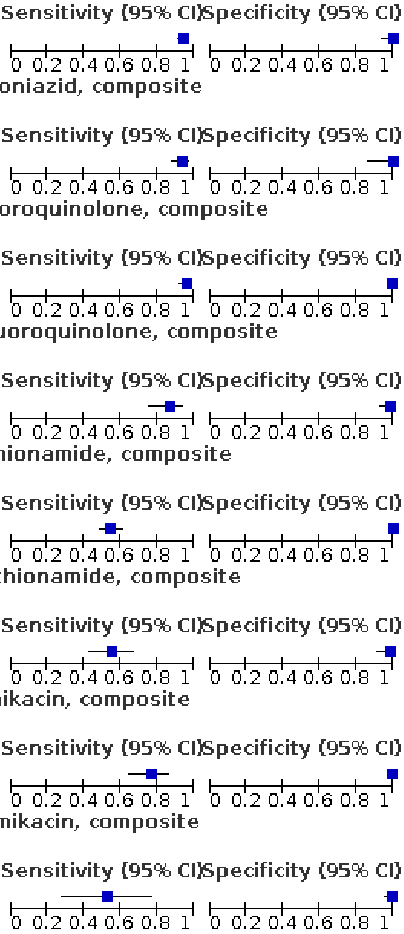
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	61	1	21	426	0.74 [0.64, 0.83]	1.00 [0.99, 1.00]



Appendix 8. Xpert MTB/XDR for detection of drug resistance by smear status

Figure 14

Figure 14. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for resistance to isoniazid, fluoroquinolone, ethionamide, and amikacin, by smear status, composite reference standard. Data were reported for all study cohorts combined. TP = true positive; FP = false positive; FN = false negative; TN = true negative.



Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	362	0	22	54	0.94 [0.91, 0.96]	1.00 [0.93, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	105	0	7	25	0.94 [0.88, 0.97]	1.00 [0.86, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	171	1	7	231	0.96 [0.92, 0.98]	1.00 [0.98, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	52	1	8	73	0.87 [0.75, 0.94]	0.99 [0.93, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	143	0	118	156	0.55 [0.49, 0.61]	1.00 [0.98, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	39	1	32	60	0.55 [0.43, 0.67]	0.98 [0.91, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-positive, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	52	1	16	335	0.76 [0.65, 0.86]	1.00 [0.98, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, smear-negative, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	9	1	8	112	0.53 [0.28, 0.77]	0.99 [0.95, 1.00]

Appendix 9. Xpert MTB/XDR for detection of drug resistance by HIV status

Figure 15

Figure 15. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for resistance to isoniazid, fluoroquinolone, ethionamide, and amikacin in HIV-positive and HIV-negative people, composite reference standard. Data were reported for all study cohorts combined. TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	53	0	2	5	0.96 [0.87, 1.00]	1.00 [0.48, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, isoniazid, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	275	0	19	46	0.94 [0.90, 0.96]	1.00 [0.92, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	15	1	0	29	1.00 [0.78, 1.00]	0.97 [0.83, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, fluoroquinolone, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	111	1	11	210	0.91 [0.84, 0.95]	1.00 [0.97, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	31	0	8	14	0.79 [0.64, 0.91]	1.00 [0.77, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, ethionamide, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	109	1	87	135	0.56 [0.48, 0.63]	0.99 [0.96, 1.00]

Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-positive, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	15	1	0	28	1.00 [0.78, 1.00]	0.97 [0.82, 1.00]

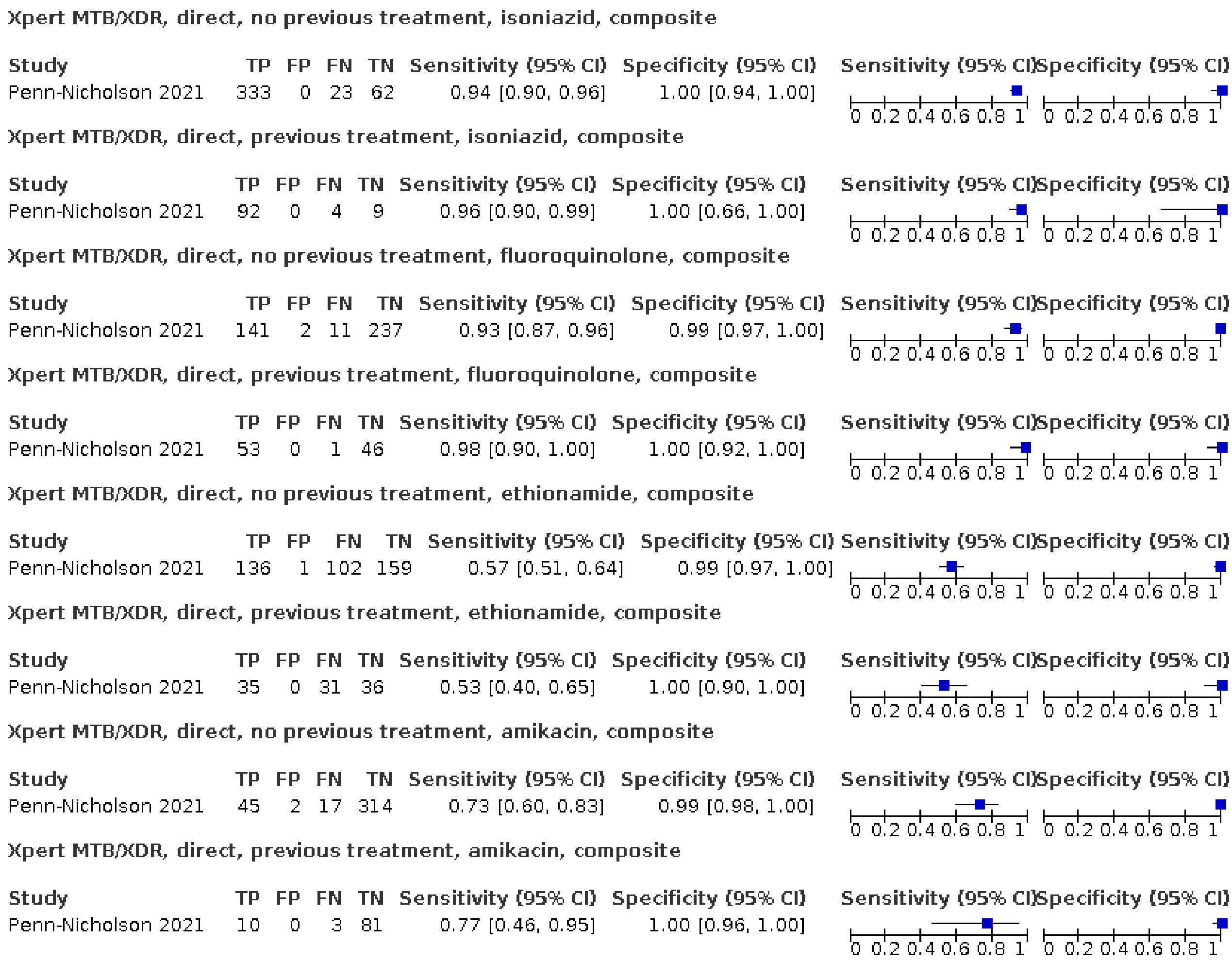
Xpert MTB/XDR, direct, irrespective of rifampicin resistance, HIV-negative, amikacin, composite

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Penn-Nicholson 2021	27	0	18	272	0.60 [0.44, 0.74]	1.00 [0.99, 1.00]

Appendix 10. Xpert MTB/XDR for detection of drug resistance in in people with and without previous treatment for tuberculosis

Figure 16

Figure 16. Forest plots of Xpert MTB/XDR sensitivity and specificity by direct testing for resistance to isoniazid, fluoroquinolone, ethionamide, and amikacin in people with and without previous treatment for tuberculosis, composite reference standard. Data were reported for all study cohorts combined. TP = true positive; FP = false positive; FN = false negative; TN = true negative.



Appendix 11. Critical concentrations and clinical breakpoints for medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis

Drug groups	Drug	LJ	7H10	7H11	MGIT
First-line drugs	Isoniazid	0.2	0.2	0.2	0.1
Fluoroquinolones	Levofloxacin (CC)	2.0	1.0	—	1.0
	Moxifloxacin (CC)	1.0	0.5	0.5	0.25
	Moxifloxacin (CB)	—	2.0	—	1.0
	Gatifloxacin (CC)	0.5	—	—	0.25

(Continued)

Second-line injectable agents	Amikacin	30.0	2.0	—	1.0
	Capreomycin	40.0	4.0	—	2.5
	Kanamycin	30.0	4.0	—	2.5
Other second-line agents	Ethionamide	40.0	5.0	10	5.0

Abbreviations: **LJ:** Löwenstein–Jensen medium; **MGIT:** Mycobacteria Growth Indicator Tube.

Table adapted from WHO Critical Concentrations 2018 and WHO Critical Concentrations 2021.

All concentrations are in mg/L and apply to the proportion method with 1% as the critical proportion. Unless otherwise stated, they are critical concentrations (CCs), as opposed to clinical breakpoints (CBs). The clinical breakpoint is used to guide individual clinical decisions in patient treatment.

MGIT is proposed as the reference method for performing DST for second-line tuberculosis agents.

HISTORY

Protocol first published: Issue 6, 2021

CONTRIBUTIONS OF AUTHORS

SP, GRD, MDV, MC, KRS, and GT drafted the review.

MC and KRS wrote the statistical analysis section.

All review authors (SP, GRD, MC, MDV, SGS, RW, KRS, and GT) read and approved the final review draft.

DECLARATIONS OF INTEREST

SP received funding from USAID, administered by the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland.

KRS received funding from USAID, administered by the WHO Global Tuberculosis Programme, Switzerland. In addition, she has received financial support from Cochrane Infectious Diseases (UK), McGill University (Canada), Baylor College of Medicine (USA), Maastricht University (the Netherlands), and the WHO Global Tuberculosis Programme (Switzerland) for the preparation of related systematic reviews and educational materials; consultancy fees from FIND, Switzerland (for the preparation of systematic reviews and GRADE tables); consultancy fees from Stellenbosch University, South Africa (for guidance on evidence syntheses), and honoraria, and travel support to attend WHO guideline meetings.

GRD received funding from USAID, administered by the WHO Global Tuberculosis Programme, Switzerland.

MC has no known conflicts of interest.

MDV is employed by the Foundation for Innovative New Diagnostics (FIND). FIND has conducted studies and published on Xpert MTB/RIF as part of a collaborative project between FIND, a Swiss non-profit, Cepheid, a US company, and academic partners. The product arising through this partnership was developed under a contract that obligated FIND to pay for development costs and trial costs and Cepheid to make the test available at specified preferential pricing to the public sector in low- and middle-income countries. In addition, FIND conducted studies for the Xpert MTB/RIF Ultra assay, which have also been published.

SGS was employed by the Foundation for Innovative New Diagnostics (FIND) while conducting the review. FIND has conducted studies and published on Xpert MTB/XDR and Xpert MTB/RIF as part of a collaborative project between FIND, a Swiss non-profit, Cepheid, a US company, and academic partners. Regarding Xpert MTB/RIF, the product developed through this partnership was developed under a contract that obligated FIND to pay for development costs and trial costs and Cepheid to make the test available at specified preferential pricing to the public sector in low- and middle-income countries. In addition, FIND conducted studies for the Xpert MTB/RIF Ultra assay, which have also been published.

RW has no known conflicts of interest.

GT received funding from USAID, administered by the WHO Global Tuberculosis Programme, Switzerland. In addition, he has received in-kind research consumable donations provided to employer by Cepheid to work on Xpert MTB/RIF and Xpert MTB/RIF Ultra (not Xpert MTB/

XDR) for diagnostic accuracy evaluations for tuberculosis detection. He is the group Principal Investigator for this work. Cepheid has also loaned instruments to conduct these studies. These studies are on different products to those potentially considered for inclusion in this Cochrane Review.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104
- World Health Organization Global Tuberculosis Programme, Switzerland

  Registration number 2020/1048818-0; purchase order 202582841

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Clinical pathway

- Scenario D. Xpert MTB/XDR used for detection of drug resistance in people being treated for pulmonary tuberculosis. We did not identify studies that assessed this role.

Objectives

- A secondary objective was to compare the diagnostic accuracy of Xpert MTB/XDR by direct testing (whereby Xpert MTB/XDR is tested directly on a sputum specimen) versus indirect testing (whereby Xpert MTB/XDR is run on an *M tuberculosis* isolate grown from culture). Our plan was to perform these analyses for those studies that made direct comparisons between test evaluations with the same participants by adding a covariate for the type of testing to the model (Takwoingi 2013). However, we only identified one study that compared Xpert MTB/XDR accuracy by direct and indirect testing. Instead, we narratively described these analyses and presented results in forest plots.

Methods

- Types of studies. We identified one report at a conference and included this report in the review.

- Conflicts of interest. We had planned to assess conflicts of interest using the Tool for Addressing Conflicts of Interest in Trials (TACIT) (Lundh 2020). However, this tool was not available while we performed the review. We extracted information about industry sponsorship and performed sensitivity analyses by repeating the meta-analyses and excluding the study sponsored by the manufacturer.

Statistical analyses

- Regarding fluoroquinolone resistance, we had planned to take the following approach. If multiple fluoroquinolones were tested by pDST and at least one was resistant, the patient would be classified as resistant. If no resistant results occurred and a least one pDST susceptible result was present, that patient would be classified as susceptible. However, none of the included studies tested more than one fluoroquinolone by pDST.

- Due to little observed variability in specificity and in the volume of analyses, we chose to present only forest plots, as such plots were more informative than corresponding summary receiver operator characteristics (SROC) plots.

- We did not perform a meta-analysis for Xpert MTB/XDR for pulmonary tuberculosis detection as heterogeneity, in terms of both characteristics of included participants and observed specificity values, would have rendered the summary sensitivity and specificity estimates uninterpretable and potentially misleading.

Inconclusive results

- We performed meta-analyses to estimate the summary proportion of non-determinate and indeterminate results using the metaprop command in Stata (Version 14) (Stata).

- We wrote in the protocol that we would extract data on discrepant analysis, where in each study, gene sequencing was applied only to resolve discordant
Xpert MTB/XDR-pDST results. However, the study cohorts evaluated Xpert MTB/XDR using both pDST and gDST as reference standards and we did not characterize discordant results further.

Investigations of heterogeneity

We had planned to explore the possible influence of the pre-specified categorical covariates, listed below, by adding these covariates to the meta-analysis models. However, data were insufficient to perform these analyses. Had we performed these analyses, we would have assessed the significance of the difference in test accuracy according to each covariate by performing a likelihood ratio test comparing models with and without covariate terms.

For detection of pulmonary tuberculosis, we had planned to investigate the following potential sources of heterogeneity.

- Smear status, smear positive or negative (we described narratively).
- HIV status, positive or negative.
- Previous tuberculosis treatment, previous treatment or no previous treatment. We changed 'History of tuberculosis treatment' (in the protocol) to 'previous tuberculosis treatment' (in the review).
- Treatment status, no treatment or currently receiving treatment.
- Treatment response status, culture conversion, yes or no.

For detection of drug resistance, we investigated the following potential sources of heterogeneity.

- Type of reference standard.
- Smear status, positive or negative (we described narratively).
- HIV status, positive or negative (we described narratively).
- Previous tuberculosis treatment, previous treatment or no previous treatment (we described narratively).

In addition, we had planned to investigate specific drugs (e.g. ofloxacin or moxifloxacin) used in the pDST reference standard for determining fluoroquinolone resistance; however data were not available to do this.

We had also planned to investigate 'Was the WHO-recommended critical drug concentration used for the pDST reference standard (WHO Critical Concentrations 2018; WHO Critical Concentrations 2021), yes or no? However, the included studies used the currently recommended concentration for each drug.

Sensitivity analyses

- For Xpert MTB/XDR for detection of drug resistance against the pDST reference standard, we had planned to perform sensitivity analyses for studies meeting the QUADAS-2 criteria listed below. However, there were only two studies in the review and the sensitivity analyses are less meaningful with few studies.

1. Was a consecutive or random sample of participants/specimens enrolled?
2. Were the reference standard results interpreted without knowledge of the results of the index test results?
3. Was the test applied in the manner recommended by the manufacturer (index test domain, low concern about applicability)?

Questions numbered 2 and 3 were satisfied by all studies.

- For Xpert MTB/XDR for detection of resistance to isoniazid and fluoroquinolones in people irrespective of rifampicin resistance, we performed sensitivity analyses by repeating the meta-analyses and excluding the study (reporting on two study cohorts) sponsored by the manufacturer. For detection of resistance to ethionamide and amikacin in people with known rifampicin resistance, we did not perform sensitivity analyses because the main analyses included only one study (reporting on four study cohorts), which was not sponsored by the manufacturer.