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[Diagnostic Test Accuracy Review]

Xpert MTB/RIF and Xpert Ultra assays for screening for pulmonary tuberculosis and rifampicin resistance in adults, irrespective of signs or symptoms

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ABSTRACT

Background

Tuberculosis is a leading cause of infectious disease-related death and is one of the top 10 causes of death worldwide. The World Health Organization (WHO) recommends the use of specific rapid molecular tests, including Xpert MTB/RIF or Xpert Ultra, as initial diagnostic tests for the detection of tuberculosis and rifampicin resistance in people with signs and symptoms of tuberculosis. However, the WHO estimates that nearly one-third of all active tuberculosis cases go undiagnosed and unreported. We were interested in whether a single test, Xpert MTB/RIF or Xpert Ultra, could be useful as a screening test to close this diagnostic gap and improve tuberculosis case detection.

Objectives

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra for screening for pulmonary tuberculosis in adults, irrespective of signs or symptoms of pulmonary tuberculosis in high-risk groups and in the general population. Screening "irrespective of signs or symptoms" refers to screening of people who have not been assessed for the presence of tuberculosis symptoms (e.g. cough).

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra for detecting rifampicin resistance in adults screened for tuberculosis, irrespective of signs and symptoms of pulmonary tuberculosis in high-risk groups and in the general population.

Search methods

We searched 12 databases including the Cochrane Infectious Diseases Group Specialized Register, MEDLINE and Embase, on 19 March 2020 without language restrictions. We also reviewed reference lists of included articles and related Cochrane Reviews, and contacted researchers in the field to identify additional studies.

Selection criteria

Cross-sectional and cohort studies in which adults (15 years and older) in high-risk groups (e.g. people living with HIV, household contacts of people with tuberculosis) or in the general population were screened for pulmonary tuberculosis using Xpert MTB/RIF or Xpert Ultra. For tuberculosis detection, the reference standard was culture. For rifampicin resistance detection, the reference standards were culture-based drug susceptibility testing and line probe assays.

Data collection and analysis

Two review authors independently extracted data using a standardized form and assessed risk of bias and applicability using QUADAS-2. We used a bivariate random-effects model to estimate pooled sensitivity and specificity with 95% credible intervals (CrIs) separately for tuberculosis detection and rifampicin resistance detection. We estimated all models using a Bayesian approach. For tuberculosis detection, we first estimated screening accuracy in distinct high-risk groups, including people living with HIV, household contacts, people residing in prisons, and miners, and then in several high-risk groups combined.

Main results

We included a total of 21 studies: 18 studies (13,114 participants) evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis and one study (571 participants) evaluated both Xpert MTB/RIF and Xpert Ultra. Three studies (159 participants) evaluated Xpert MTB/RIF for rifampicin resistance. Fifteen studies (75%) were conducted in high tuberculosis burden and 16 (80%) in high TB/HIV-burden countries. We judged most studies to have low risk of bias in all four QUADAS-2 domains and low concern for applicability.

Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis

In people living with HIV (12 studies), Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 61.8% (53.6 to 69.9) (602 participants; moderate-certainty evidence) and 98.8% (98.0 to 99.4) (4173 participants; high-certainty evidence). Of 1000 people where 50 have tuberculosis on culture, 40 would be Xpert MTB/RIF-positive; of these, 9 (22%) would not have tuberculosis (false-positives); and 960 would be Xpert MTB/RIF-negative; of these, 19 (2%) would have tuberculosis (false-negatives).

In people living with HIV (1 study), Xpert Ultra sensitivity and specificity (95% CI) were 69% (57 to 80) (68 participants; very low-certainty evidence) and 98% (97 to 99) (503 participants; moderate-certainty evidence). Of 1000 people where 50 have tuberculosis on culture, 53 would be Xpert Ultra-positive; of these, 19 (36%) would not have tuberculosis (false-positives); and 947 would be Xpert Ultra-negative; of these, 16 (2%) would have tuberculosis (false-negatives).

In non-hospitalized people in high-risk groups (5 studies), Xpert MTB/RIF pooled sensitivity and specificity were 69.4% (47.7 to 86.2) (337 participants, low-certainty evidence) and 98.8% (97.2 to 99.5) (8619 participants, moderate-certainty evidence). Of 1000 people where 10 have tuberculosis on culture, 19 would be Xpert MTB/RIF-positive; of these, 12 (63%) would not have tuberculosis (false-positives); and 981 would be Xpert MTB/RIF-negative; of these, 3 (0%) would have tuberculosis (false-negatives).

We did not identify any studies using Xpert MTB/RIF or Xpert Ultra for screening in the general population.

Xpert MTB/RIF as a screening test for rifampicin resistance

Xpert MTB/RIF sensitivity was 81% and 100% (2 studies, 20 participants; very low-certainty evidence), and specificity was 94% to 100%, (3 studies, 139 participants; moderate-certainty evidence).

Authors' conclusions

Of the high-risks groups evaluated, Xpert MTB/RIF applied as a screening test was accurate for tuberculosis in high tuberculosis burden settings. Sensitivity and specificity were similar in people living with HIV and non-hospitalized people in high-risk groups. In people living with HIV, Xpert Ultra sensitivity was slightly higher than that of Xpert MTB/RIF and specificity similar. As there was only one study of Xpert Ultra in this analysis, results should be interpreted with caution. There were no studies that evaluated the tests in people with diabetes mellitus and other groups considered at high-risk for tuberculosis, or in the general population.

PLAIN LANGUAGE SUMMARY

How accurate are sputum Xpert tests for screening for active pulmonary tuberculosis and rifampicin resistance in adults whether or not they have tuberculosis symptoms?

Why is using Xpert tests to screen for pulmonary tuberculosis important?

Tuberculosis is the leading cause of infectious disease-related death and one of the top 10 causes of death worldwide. The World Health Organization (WHO) recommends using specific rapid tests as initial tests for diagnosing tuberculosis and rifampicin resistance in people with signs and symptoms of tuberculosis. However, the WHO estimates that nearly one-third of all active tuberculosis cases go undiagnosed and unreported. Not recognizing tuberculosis when it is present (a false negative test result) may result in illness and death and an increased

risk of infecting others. An incorrect diagnosis of tuberculosis (false-positive result) may mean that people are given antibiotics when there is no benefit to be gained.

What is the aim of this review?

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis and rifampicin resistance in adults whether or not they have tuberculosis symptoms (such as cough, fever, weight loss, and night sweats). We were interested in how the tests worked in groups at high risk for tuberculosis, including people living with HIV (PLHIV), household contacts of people with tuberculosis, miners, people residing in prisons, people with diabetes, and in the general public.

What was studied in this review?

Xpert MTB/RIF and Xpert Ultra are rapid tests for simultaneously diagnosing tuberculosis and rifampicin resistance. We combined study results to determine:

- sensitivity: people with tuberculosis (rifampicin resistance) correctly diagnosed as having the condition.

- specificity: people without tuberculosis (rifampicin resistance) correctly identified as not having the condition.

The closer sensitivity and specificity are to 100%, the better the test.

What are the main results in this review?

Twenty-one studies: 18 studies (13,114 participants) evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis and one study (571 participants) evaluated both Xpert MTB/RIF and Xpert Ultra. Three studies (159 participants) evaluated Xpert MTB/RIF for rifampicin resistance.

For every 1000 people tested, if 50 had tuberculosis according to the reference standard:

PLHIV

- Xpert MTB/RIF (12 studies):

· 40 people would test positive, including 9 without tuberculosis (62% sensitivity)

· 960 people would test negative, including 19 with tuberculosis (99% specificity)

- Xpert Ultra (1 study):

· 53 people would test positive, including 19 without tuberculosis (69% sensitivity)

· 947 people would test negative, including 16 with tuberculosis (98% specificity)

For every 1000 people tested, if 10 had tuberculosis according to the reference standard:

Other high-risk groups combined

- Xpert MTB/RIF (5 studies):

· 19 people would test positive, including 12 without tuberculosis (69% sensitivity)

· 981 people would test negative, including 3 with tuberculosis (99% specificity)

For detection of rifampicin resistance, Xpert MTB/RIF sensitivity was 81% and 100% (2 studies) and specificity was 94% to 100% (3 studies).

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

In the included studies, the reference standards for diagnosing pulmonary tuberculosis (culture) and rifampicin resistance (drug susceptibility testing) are likely to have been reliable methods for deciding whether patients really had the conditions. We were fairly confident in the results for Xpert MTB/RIF in PLHIV, and less so for other high-risk groups. Not enough people have been studied to be confident about the results for Xpert Ultra or for detection of rifampicin resistance.

Who do the results of this review apply to?

Studies were mainly performed in high tuberculosis and high HIV burden settings. No studies evaluated the tests in people with diabetes mellitus or the general population.

What are the implications of this review?

In PLHIV, Xpert MTB/RIF as a screening test was accurate for tuberculosis in high tuberculosis burden settings. In high-risk groups, Xpert MTB/RIF may assist in identifying tuberculosis, but the certainty of evidence is low. In PLHIV, Xpert Ultra sensitivity was slightly higher than that of Xpert MTB/RIF and specificity similar based on one study. There were few studies and few people tested for rifampicin resistance and no studies that evaluated the tests in people with diabetes or in the general population.

How up-to-date is this review?

19 March 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Xpert MTB/RIF as a screening test for pulmonary tuberculosis in people living with HIV and non-hospitalized people in high-risk groups

Review question: what is the accuracy of Xpert MTB/RIF and Xpert Ultra for screening for pulmonary tuberculosis in adults irrespective of signs or symptoms of pulmonary tuberculosis?
Patients/population: people living with HIV and non-hospitalized people in high-risk groups

Setting: community and primary care facilities
Index tests: Xpert MTB/RIF and Xpert Ultra; **role**: screening test
Threshold for index tests: an automated result is provided
Reference standards: solid or liquid culture
Studies: cross-sectional and cohort studies

Index test, population	Effect (95% CrI)	Number of participants (studies)	Test result	Number of results per 1000 patients tested (95% CI)			Certainty of the evidence (GRADE)
				Prevalence 0.5%	Prevalence 5%	Prevalence 10%	
Xpert MTB/RIF, people living with HIV	Pooled sensitivity 61.8% (53.6 to 69.9)	602 (12)	True positives	3 (3 to 3)	31 (27 to 35)	62 (54 to 70)	⊕⊕⊕◯ Moderate[a,b]
			False negatives	2 (2 to 2)	19 (15 to 23)	38 (30 to 46)	
	Pooled specificity 98.8% (98.0 to 99.4)	4173 (12)	True negatives	985 (975 to 985)	941 (931 to 941)	891 (882 to 891)	⊕⊕⊕⊕ High
			False positives	10 (10 to 20)	9 (9 to 19)	9 (9 to 18)	
Xpert Ultra, people living with HIV	Sensitivity 69% (57 to 80)	68 (1)	True positives	3 (3 to 4)	34 (28 to 40)	69 (57 to 80)	⊕◯◯◯[c,d] Very low
			False negatives	2 (1 to 2)	16 (10 to 22)	31 (20 to 43)	
	Specificity 98% (97 to 99)	503 (1)	True negatives	975 (965 to 985)	931 (922 to 941)	882 (873 to 891)	⊕⊕⊕◯[c] Moderate
			False positives	20 (10 to 30)	19 (9 to 28)	18 (9 to 27)	
				Prevalence 0.5%	**Prevalence 1%**	**Prevalence 2%**	**Certainty of the evidence (GRADE)**
Xpert MTB/RIF, non-hospitalized people in high-risk groups	Pooled sensitivity 69.4% (47.7 to 86.2)	337 (5)	True positives	3 (2 to 4)	7 (5 to 9)	14 (10 to 17)	⊕⊕◯◯[e,f,g] Low
			False negatives	2 (1 to 3)	3 (1 to 5)	6 (3 to 10)	

	Pooled specificity 98.8% (97.2 to 99.5)	8619 (5)	True negatives	983 (967 to 990)	978 (962 to 985)	968 (953 to 974)	⊕⊕⊕◯[e] Moderate
			False positives	12 (5 to 28)	12 (5 to 28)	12 (5 to 27)	

Abbreviations: CI: confidence interval; CrI: credible interval; IQR: interquartile range.
Prevalence estimates were suggested by the WHO Global TB Programme. For Xpert MTB/RIF, the median prevalence of tuberculosis in the included studies was 12.5% (IQR 9.8% to 15.4%). For Xpert Ulta, the prevalence of tuberculosis was 11.9%.
95% credible limits were estimated based on those around the point estimates for pooled sensitivity and specificity; 95% confidence intervals were estimated for true positives, false negatives, true negatives, and false positives.
Explanations
[a]Most studies were conducted in high-tuberculosis burden settings. Applicability to settings with lower tuberculosis prevalence comes with some uncertainty. This was a judgment; we did not downgrade for indirectness.
[b]For individual studies, sensitivity ranged from 43% to 100%. We thought that heterogeneity could be explained in part by the percentage of patients with tuberculosis symptoms, differences in CD4 count, and hospitalized versus outpatient status. We downgraded one level for inconsistency.
[c]Only one study contributed to this estimate. South Africa is the only country represented. Applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.
[d]The 95% CI is wide. There was a low number of participants contributing to the analysis for the observed sensitivity. We downgraded two levels for imprecision.
[e]"Non-hospitalized people in high risk groups" is a broad category comprising adults with multiple geographic, occupational, environmental, clinical, and behavioral risk factors for tuberculosis. Studies contributing to this pooled estimate included household contacts of persons with tuberculosis, adults in prison, and miners. There is some uncertainty associated with applicability to other high-risk groups. Additionally, one of the studies included a small number of children (age < 15) in the screened population, which deviates from the intended study population. We downgraded one level for indirectness.
[f]Sensitivity estimates ranged from 33% to 100%. We thought this variability could partly be explained by the different high-risk groups in this analysis. We downgraded one level for inconsistency.
[g]The 95% CrI is wide. We thought the 95% CrI around true positives and false negatives would likely lead to different decisions depending on which limits are assumed. As we had already downgraded for inconsistency, we did not downgrade further 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. Xpert MTB/RIF for detecting rifampicin resistance for high-risk groups

Review question: what is the accuracy of Xpert MTB/RIF and Xpert Ultra for screening for rifampicin resistance in adults irrespective of signs or symptoms of pulmonary tuberculosis?
Patients/population: people in high-risk groups

Setting: community and primary care facilities
Index tests: Xpert MTB/RIF and Xpert Ultra (no studies identified using Xpert Ultra); **role**: screening test
Threshold for index tests: an automated result is provided
Reference standards: phenotypic culture-based drug susceptibility testing and line probe assays

Studies: cross-sectional and cohort studies

Index test	Effect	Number of participants (studies)	Test result	Number of results per 1000 patients tested			Certainty of the evidence (GRADE)
				Prevalence 0.5%	Prevalence 1%	Prevalence 2%	
Xpert MTB/RIF	Sensitivity 81% and 100%	20 (2)	True positives	4 to 5	8 to 10	16 to 20	⊕◯◯◯[a,b,c] Very low
			False negatives	0 to 1	0 to 2	0 to 4	
	Specificity 94% to 100%	139 (3)	True negatives	935 to 995	931 to 990	921 to 980	⊕⊕⊕◯[d,e] Moderate
			False positives	0 to 60	0 to 59	0 to 59	

Prevalence estimates were suggested by the WHO Global TB Programme. The prevalence of rifampicin resistance in the studies was 7.3% and 16.7%.

Explanations

[a]There were only two studies included in this analysis, conducted in sub-Saharan Africa. The prevalence of rifampicin resistance in the studies was higher than those presented in the table. The applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

[b]There was a wide range of sensitivities of Xpert MTB/RIF for detection of rifampicin resistance between the two included studies: 81% and 100%. We downgraded one level for inconsistency.

[c]There were few participants contributing to this analysis. We already downgraded one level for inconsistency. We downgraded one level for imprecision.

[d]Of the three included studies, two were conducted in southern Africa, one in Malaysia. Applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.

[e]The specificities were 94%, 97%, and 100%. One explanation for the lower specificity of 94% is a problem identified with the Xpert MTB/RIF assay, which was modified to improve specificity after publication of this study. We did not downgrade 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

Tuberculosis is the world's leading cause of infectious disease-related death and is one of the top 10 causes of death worldwide. In 2019, an estimated 10 million people developed tuberculosis disease (WHO Global TB Report 2020).

Among all tuberculosis cases, about 8% were in people living with HIV (WHO Global TB Report 2020). The risk of developing tuberculosis is much higher in people living with HIV, estimated to be 20 to 37 times higher in HIV-positive individuals than in HIV-negative individuals (Getahun 2010). Signs and symptoms of tuberculosis in people living with HIV vary, which makes it challenging to determine when to consider a diagnosis of tuberculosis - tuberculosis is the leading cause of hospitalisation and death in people with HIV worldwide (Ford 2016). In addition, there were around 500,000 new cases of rifampicin-resistant tuberculosis, of which 78% had multidrug-resistant tuberculosis (tuberculosis that is resistant to both rifampicin and isoniazid, the two most essential anti-tuberculosis drugs) (WHO Global TB Report 2020). When tuberculosis is detected early and is effectively treated, the disease is largely curable. Ending the tuberculosis epidemic by 2030 is among the health-related targets described in United Nations Sustainable Development Goal 3 (WHO END TB 2015). The United Nations Sustainable Development Goals represent a collective plan to end poverty, decrease inequality, and protect the planet from degradation by 2030 (UN Sustainable Development Goals 2030).

The World Health Organization (WHO) recommends the use of specific rapid molecular tests, including Xpert MTB/RIF or Xpert Ultra, the newest version of the assay, as the initial diagnostic tests for the detection of tuberculosis and rifampicin resistance in people with signs and symptoms of tuberculosis (WHO Consolidated Guidelines (Module 3) 2020). However, the WHO estimates that nearly one-third of all active tuberculosis cases go undiagnosed and unreported (WHO Global TB Report 2020). In an effort to close this diagnostic gap, the WHO is seeking evidence to recommend case-finding approaches and strategies to improve tuberculosis case detection of the 'missing millions'. In particular, the WHO is interested in case-finding approaches in high-risk groups and settings, such as people living with HIV, people with diabetes mellitus, and people residing in prisons. Stated another way, the WHO is interested in the best ways to find the so-called 'missing millions'.

Tuberculosis screening is a term that has been used differently in the literature depending on the context. We use tuberculosis screening as defined by the WHO: the "systematic identification of people with suspected active TB [tuberculosis], in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly." Further, we define intensified case-finding as tuberculosis screening activities set in health facilities, and active case-finding as tuberculosis screening activities set in the community, including household-based or residence-based screening activities (WHO Systematic screening 2013). The End-TB strategy emphasizes early diagnosis of tuberculosis, including universal drug susceptibility testing, and systematic screening of contacts and high-risk groups (WHO Global TB Report 2020).

Current screening approaches for active tuberculosis typically recommend initial screening of people living with HIV for four cardinal signs and symptoms of tuberculosis: cough, fever, weight loss, and night sweats, or people who do not have HIV, the single symptom of prolonged cough. People with a positive symptom screen then may go on to receive additional screening with a chest X-ray and diagnostic testing using sputum Xpert MTB/RIF or Xpert Ultra as recommended. Concerning people living with HIV, a recent systematic review found that the four-symptom screen had lower sensitivity and specificity for active tuberculosis in HIV-positive people on antiretroviral therapy (ART) than in HIV-positive people not taking ART (Hamada 2018). Compared to Xpert MTB/RIF, Xpert Ultra has shown increased sensitivity for tuberculosis in HIV-positive people (Dorman 2018). WHO Tuberculosis Standard 8 states, "For persons living with HIV, the Xpert MTB/RIF Ultra assay should be used as an initial diagnostic test" (WHO Compendium of WHO guidelines 2018). Recent population surveys using chest radiography, irrespective of symptoms, as the initial screen for tuberculosis (followed by diagnostic testing) have identified a substantial burden of subclinical tuberculosis in people with and without HIV, supporting a need for new approaches to screen and identify active tuberculosis using more sensitive tools (Frascella 2020; Gunasekera 2020).

Several Cochrane Reviews have been published or are in process to assess the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for different target conditions and in various populations. Of relevance to the current review, recent Cochrane Reviews found Xpert MTB/RIF and Xpert Ultra to be highly sensitive and specific for pulmonary tuberculosis and rifampicin resistance in adults with signs and symptoms of tuberculosis; see Index test(s) (Horne 2019; Zifodya 2021). The current review determined the accuracy of Xpert MTB/RIF and Xpert Ultra for tuberculosis and rifampicin resistance in adults, irrespective of signs and symptoms of tuberculosis, that is, when used as a screening test. Screening "irrespective of signs or symptoms" refers to screening of people who have not been assessed for the presence of tuberculosis symptoms (e.g. cough). This can include both asymptomatic (people without symptoms of tuberculosis) and people with symptoms of tuberculosis.

Target condition being diagnosed

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis (M tuberculosis)* and is spread from person to person through the air. Tuberculosis most commonly affects the lungs (pulmonary tuberculosis), but may affect any organ or tissue outside of the lungs (extrapulmonary tuberculosis). Signs and symptoms of pulmonary tuberculosis include cough, fever, chills, night sweats, weight loss, haemoptysis (coughing up blood), and fatigue. Signs and symptoms of extrapulmonary tuberculosis depend on the site of disease. Tuberculosis treatment regimens must contain multiple drugs, to which the organisms are sensitive, to cure tuberculosis and avoid selection for drug resistance. In 2019, there were approximately half a million new cases of rifampicin-resistant tuberculosis, of which 78% were multidrug-resistant (MDR-TB) (WHO Global TB Report 2020), The treatment of MDR-TB is complex, historically requiring two years or more of therapy, although the WHO conditionally recommended a regimen of nine to 12 months in 2016 (WHO Guidelines 2016). The drugs used to treat MDR-TB are less potent and more toxic than the drugs used to treat drug-susceptible tuberculosis. WHO guidance states that "All patients with MDR-TB or rifampicin-resistant tuberculosis, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under

programmatic conditions" (WHO Consolidated Guidelines (Module 4) 2020).

Index test(s)

Xpert MTB/RIF is an automated polymerase chain reaction (PCR) test (molecular test) using the GeneXpert platform (Cepheid 2019). Xpert MTB/RIF is a single test that can detect both *M tuberculosis* complex and rifampicin resistance within two hours after starting the test, with minimal hands-on technical time. Unlike conventional nucleic acid amplification tests, (NAATs), Xpert MTB/RIF integrates sample processing and PCR amplification and detection into a single cartridge. Following sample loading, all steps in the assay are completely automated and self-contained. In addition, the assay's sample reagent, used to liquefy sputum, has potent tuberculocidal (the ability to kill tuberculosis bacteria) properties and so largely eliminates biosafety concerns during the test procedure (Banada 2010). Xpert MTB/RIF requires an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules (Global Laboratory Initiative 2019).

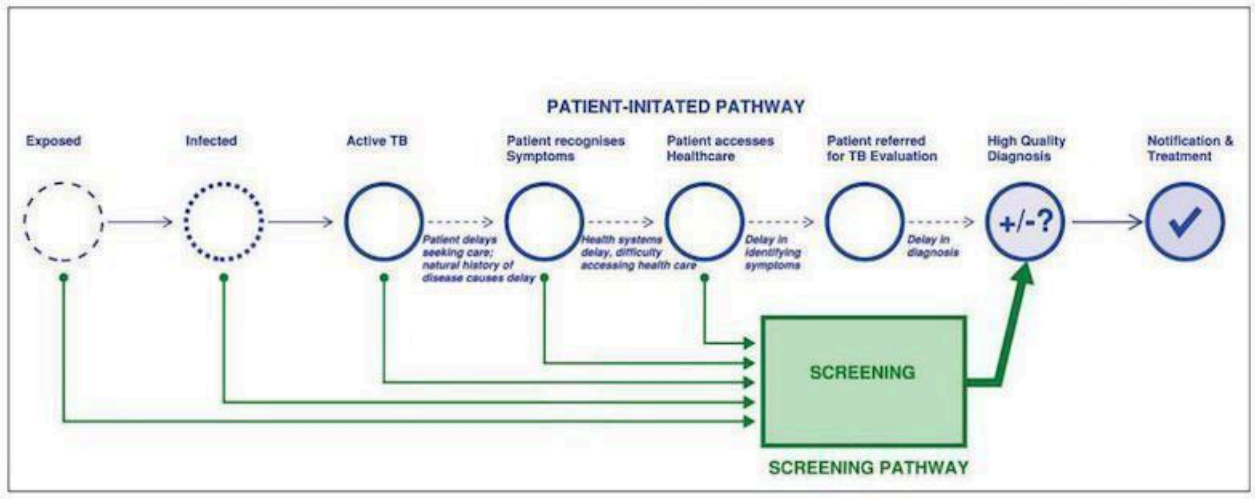
Since Xpert MTB/RIF was released, there have been four generations of the test (G1, G2, G3, and G4), involving different software and cartridge combinations. G4 contains modifications that improved determination of rifampicin resistance detection as previous Xpert MTB/RIF versions had found that some rifampicin susceptibility results were falsely resistant. Our previous review identified considerable overlap of the accuracy estimates for Xpert MTB/RIF across generations of the test, suggesting that the difference in test generations was unlikely to contribute meaningfully to heterogeneity in accuracy estimates (Steingart 2014). In order to improve on Xpert MTB/RIF sensitivity, Cepheid developed Xpert MTB/RIF Ultra (hereafter referred to as Xpert Ultra), a re-engineered assay that uses a newly developed cartridge but may be run on the same device after a software upgrade. Xpert Ultra incorporates two different multi-copy amplification targets and a larger DNA reaction chamber than Xpert MTB/RIF (WHO Xpert Ultra 2017). A laboratory study reported that the limit of detection using Xpert Ultra improved to 15.6 CFU/mL of sputum compared to 112.6 CFU/mL for Xpert MTB/RIF (Chakravorty 2017). Of note, Xpert Ultra has added a new result category, 'trace call', that corresponds to the lowest bacillary burden for *M tuberculosis* detection (WHO Xpert Ultra 2017). Although no result for rifampicin resistance will be available for people with trace results, a trace-positive result is sufficient to initiate anti-tuberculosis therapy in children or HIV-positive people, according to the WHO report. Xpert Ultra is available for clinical use and several countries have moved from using Xpert MTB/RIF to using Xpert Ultra instead. In this Cochrane Review, we included studies that used any generation of the index tests.

Regarding the accuracy of Xpert MTB/RIF and Xpert Ultra for diagnosis of pulmonary tuberculosis in people with signs and symptoms, a recent Cochrane Review found pooled sensitivity and specificity (95% credible interval) against culture were 90.9% (86.2 to 94.7) and 95.6% (93.0 to 97.4) for Xpert Ultra (7 studies, 2834 participants; high-certainty evidence) and 84.7% (78.6 to 89.9) and 98.4% (97.0 to 99.3) for Xpert MTB/RIF (7 studies, 2835 participants; high-certainty evidence), For detection of rifampicin resistance, pooled sensitivity and specificity were 94.9% (88.9 to 97.9) and 99.1% (97.7 to 99.8) for Xpert Ultra (5 studies, 921 participants; high-certainty evidence) versus 95.3% (90.0 to 98.1) and 98.8% (97.2 to 99.6) for Xpert MTB/RIF (5 studies, 930 participants; high-certainty evidence) (Zifodya 2021).

Clinical pathway

There are two complementary approaches to detection of active tuberculosis, Figure 1. The first is the patient-initiated pathway, also known as passive case finding. The second is the provider-initiated screening pathway, which represents the analytic framework for this review (WHO Systematic screening 2015). The index test, either Xpert MTB/RIF or Xpert Ultra, would be performed as the only test for pulmonary tuberculosis and rifampicin resistance in adults, irrespective of signs or symptoms of pulmonary tuberculosis, in high-risk groups and in primary health facilities or community settings.

Figure 1. There are two complementary approaches to detection of active tuberculosis. The first is the patient-initiated pathway, also known as passive case finding. The second is the provider-initiated screening pathway (WHO Systematic screening 2015), which represents the analytic framework for this review. In the latter pathway, the index test would be applied as the only test, to adults, irrespective of signs and symptoms of tuberculosis, in high-risk groups and in primary health facilities or community settings.



The purpose of the index tests is screening.

The role of the index tests is replacement for usual practice. This may include replacement for the WHO four-question symptom screen.

The downstream consequences of screening include the following.

- True-positive (TP): patients would benefit from rapid diagnosis and initiation of appropriate treatment.
- True-negative (TN): patients would be spared unnecessary treatment and would benefit from reassurance, pursuit of an alternative diagnosis if they have symptoms, and determination of eligibility for tuberculosis preventive therapy if indicated.
- False-positive (FP): patients would probably experience anxiety and morbidity caused by additional testing, unnecessary treatment, and possible adverse events; possible stigma associated with a tuberculosis or MDR-TB diagnosis; and the chance that a false-positive result may halt further diagnostic evaluation of the true underlying condition.
- False-negative (FN): patients would experience an increased risk of morbidity and mortality, and delayed or inappropriate treatment initiation; there would be risk of ongoing tuberculosis transmission.

Alternative test(s)

Alternative screening tests for tuberculosis include no screening (or passive case-finding), and one or more of symptom screening (such as the WHO four-question symptom screen) and chest X-ray, which must be further confirmed with a diagnostic test. Other tools that may be useful in screening include urine lipoarabinomannan (LAM) testing and smear microscopy, which require additional definitive drug resistance testing even if used as simultaneous screening and diagnostic tests. We have previously described selected alternative tests for detection of pulmonary tuberculosis and rifampicin resistance (Horne 2019; Lewinsohn 2017; Unitaid 2017). A Special Collection curated by Cochrane contributors includes Cochrane Reviews from Cochrane Infectious Diseases and other systematic reviews from other international teams. The Special Collection describes key WHO guidelines on tuberculosis diagnostics, and their underpinning systematic reviews (Cochrane Special Collection 2020). Below we review screening tools and highlight several recent developments in tuberculosis diagnostics.

Numerous symptoms, singly and in combination, have been proposed to screen for tuberculosis in different settings. A healthcare or community worker asks the person being screened if they are experiencing any of the selected symptoms, and those who report symptoms according to local criteria go on to receive additional testing such as chest X-ray or diagnostic testing. The most commonly assessed symptoms are cough (varying duration), fever, weight loss, drenching night sweats, loss of appetite, haemoptysis, and fatigue. Single symptoms have modest to low sensitivity; defining a positive screen as any one or more of multiple symptoms improves sensitivity but reduces specificity, consequently increasing the number of diagnostic confirmatory tests. Accuracy of symptom screening varies with the HIV status of the people screened. One study found that any one of cough of any duration, fever of any duration, or night sweats lasting three or more weeks was the most sensitive combination of symptoms for identification of tuberculosis in people living with HIV (93% sensitivity, 36% specificity; Cain 2010). In mixed HIV-positive and HIV-negative populations, a single symptom of cough of greater than two weeks' duration identified 35% (95% confidence interval (CI) 24 to 46) of adults with culture-positive pulmonary tuberculosis in one systematic review and modelling analysis; any one of a list of tuberculosis symptoms had 70% sensitivity and 61% specificity for pulmonary tuberculosis in low-HIV-prevalence settings (van't Hoog 2013).

Chest X-ray can involve posterior-anterior, anterior-posterior, or lateral recording, or a combination of two or all of these. Major types of chest X-ray include conventional chest X-ray (producing 36

cm x 43 cm film), digital radiography, and computed radiography. Chest X-ray findings including hilar lymphadenopathy, cavitary lesions, and evidence of granulomas can all suggest pulmonary tuberculosis, but are also nonspecific and must be confirmed with additional testing. Accurate interpretation of pulmonary tuberculosis findings on chest X-ray are dependent on the ability of the individual interpreting the chest X-ray, and wide inter-observer variation has been reported (Zellweger 2006). Computer-aided interpretation of chest X-ray for pulmonary tuberculosis is a promising new technology, especially for resource-limited settings where expertise in chest X-ray interpretation is limited (Harris 2019).

Smear microscopy is the examination of smears for acid-fast bacilli (tuberculosis bacteria) under a microscope. The examination may be performed by light microscopy (Ziehl-Neelsen), fluorescence microscopy, or light-emitting diode (LED) fluorescence microscopy. Microscopy cannot distinguish between drug-susceptible tuberculosis and drug-resistant tuberculosis. The WHO recommends that microscopy, as the initial diagnostic test, should be replaced with WHO-recommended rapid tests that can simultaneously detect tuberculosis and tuberculosis drug resistance (WHO Consolidated Guidelines (Module 3) 2020).

Nucleic acid amplification tests (NAATs) are molecular systems that can detect small quantities of genetic material (DNA or RNA) from micro-organisms, such as *M tuberculosis*. The key advantage of NAATs is that they are rapid diagnostic tests, potentially providing results in a few hours. Several new commercial NAATs are in the diagnostic pipeline or have recently come to market (e.g. Truenat MTB, Truenat MTBplus, and Truenat MTB-RIF Dx, Molbio Diagnostics, India). Truenat MTB and Truenat MTB Plus assays show comparable accuracy with Xpert MTB/RIF and Xpert Ultra for detection of tuberculosis, and for sequential detection of rifampicin resistance (Truenat MTB-Rif Dx) (WHO Consolidated Guidelines (Module 3) 2020).

Alere Determine TB LAM Ag (AlereLAM, Alere Inc, Waltham, USA) is a commercially available, point-of-care test for tuberculosis disease (pulmonary and extrapulmonary tuberculosis). The test detects lipoarabinomannan (LAM), a component of the bacterial cell wall, which is present in the urine of some people with tuberculosis. AlereLAM is performed by placing urine on one end of a test strip, with results appearing as a band on the strip if tuberculosis is present. The test is simple, requires no special equipment, and shows results in 25 minutes (Bjerrum 2019). In two randomized trials, the use of Alere LAM in HIV-positive inpatients has been shown to reduce mortality (Gupta-Wright 2018; Peter 2016). Based on evidence from the randomized trials and a Cochrane Review (Bjerrum 2019), the WHO recommends that AlereLAM should be used to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents and children. The full recommendations, which differ for inpatients and outpatients, are described here: (WHO Consolidated Guidelines (Module 3) 2020).

Fujifilm SILVAMP TB LAM (FujiLAM, co-developed by Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland and Fujifilm, Tokyo, Japan) is a new, urine-based, point-of-care test for tuberculosis diagnosis in people living with HIV. In an individual participant data meta-analysis that included five cohorts of people living with HIV, FujiLAM was found to have superior sensitivity, 70.7% (95% CI 59.0% to 80.8%), compared to AlereLAM sensitivity of 42.3% (31.7% to 51.8%), against a microbiological reference standard; FujiLAM had lower specificity, 90.9% (87.2% to 93.7%), compared to AlereLAM specificity of 95.3% (92.2% to 97.7%) (Broger 2020).

Alternative molecular methods for drug susceptibility testing include the commercial line probe assays, GenoType MTBDR*plus* assay (MTBDR*plus,* Hain LifeScience, Nehren, Germany), and the Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan), which detect the presence of mutations associated with drug resistance to isoniazid and rifampicin (WHO Consolidated Guidelines (Module 3) 2020). Advantages of line probe assays are that they can provide a result for detection of tuberculosis and drug resistance in one to two days. Drawbacks are that line probe assays are expensive and need to be used in intermediate and central laboratories (Unitaid 2017).

Rationale

Since 2010, the WHO has recommended the use of Xpert MTB/RIF as the preferred initial diagnostic test for people thought to have MDR-TB or HIV-associated tuberculosis (WHO 2011). In 2013, the WHO expanded the recommendations, stating that Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected of having tuberculosis (conditional recommendation acknowledging resource implications, high-quality evidence; WHO Xpert MTB/RIF 2013). In addition, the WHO recommended that following an Xpert MTB/RIF test that demonstrates rifampicin resistance, subsequent drug susceptibility testing (e.g. using a line probe assay for second-line drugs) remains essential to detect resistance to drugs other than rifampicin (WHO Xpert MTB/RIF 2013). In 2017, based on a non-inferiority analysis of Xpert Ultra compared with Xpert MTB/RIF (Dorman 2018), the WHO stated that recommendations on the use of Xpert MTB/RIF also apply to the use of Xpert Ultra as the initial diagnostic test for all adults and children with signs and symptoms of tuberculosis (WHO Consolidated Guidelines (Module 3) 2020).

Given the demonstrated success of rapid molecular tests for diagnosing tuberculosis, we were interested whether a single test, Xpert MTB/RIF or Xpert Ultra, can be useful as a screening test to identify people with active pulmonary tuberculosis in high-risk groups and the in the general population. The settings were community settings or healthcare settings attended for reasons unrelated to tuberculosis. This is a different approach than diagnosing active tuberculosis in people with signs and symptoms of tuberculosis who seek care in health facilities. We performed this Cochrane Review to inform an updated WHO policy on tuberculosis screening, *2020 Revision of the Guidelines for Systematic Screening for Active Tuberculosis: Updated and Consolidated Recommendations and Implementation Guidance* (WHO Rapid Communication 2020). The 2020 WHO guidelines also include Cochrane and non-Cochrane systematic reviews on symptom screening, chest radiography, and other tests and strategies for screening for tuberculosis in adults and children.

OBJECTIVES

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra for screening of pulmonary tuberculosis in adults in the following high-risk groups.

- People living with HIV.
- Household contacts of people with tuberculosis.
- People residing in prisons.

- Miners.
- Patients residing in high tuberculosis burden settings attending primary health facilities.
- People experiencing homelessness.
- People with diabetes mellitus.
- People who abuse alcohol.
- People who smoke.
- Healthcare workers.

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra for screening for tuberculosis in adults, irrespective of signs or symptoms of pulmonary tuberculosis in the general population (i.e. low-risk population).

To estimate the accuracy of Xpert MTB/RIF and Xpert Ultra for the detection of rifampicin resistance in the high-risk groups and settings described above and in the general population.

Secondary objectives

To compare the accuracy of Xpert MTB/RIF and Xpert Ultra in the above high-risk groups and settings and in the general population.

To investigate potential sources of heterogeneity in accuracy estimates, including the percentage of participants with tuberculosis symptoms, tuberculosis burden, and tuberculosis/HIV burden (tuberculosis detection), and MDR-TB burden (rifampicin resistance detection).

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional studies and cohort studies that estimated the accuracy of one or both index tests for both pulmonary tuberculosis and rifampicin resistance or pulmonary tuberculosis alone. We used abstracts to identify published studies and included the full publications when they met our inclusion criteria. We only included studies that reported data comparing the index test(s) to an acceptable reference standard from which we could extract true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values. The index tests could be assessed alone or together with other tests. We included studies designed to find people with active tuberculosis in community settings. We included abstracts with sufficient data to populate a 2x2 contingency table.

We excluded case reports and studies with a case-control design, the latter because these types of studies are prone to bias, in particular, studies enrolling participants with severe disease and healthy participants without disease. We excluded drug resistance surveys.

Participants

Adults, defined as 15 years of age and older, irrespective of signs or symptoms of pulmonary tuberculosis in high-risk groups and in the general population. High-risk groups included the following:

- People living with HIV.
- Household contacts of people with tuberculosis.
- People residing in prisons.
- Miners.
- Patients attending primary health facilities.
- Homeless people.
- People with diabetes mellitus.
- People who abuse alcohol.
- Smokers.
- Healthcare workers.

The settings of interest were primary healthcare facilities and other community settings.

We excluded studies that selected participants for enrolment based on the results of prior tuberculosis testing, such as symptom screening or chest radiography.

Index tests

The index test were sputum Xpert MTB/RIF and sputum Xpert Ultra. Test results are automatically generated (i.e. there is a single threshold), and the user is provided with a printable test result as follows.

Xpert MTB/RIF (Cepheid 2019)

- MTB (*M tuberculosis*) DETECTED; RIF (rifampicin) Resistance DETECTED
- MTB DETECTED; RIF Resistance NOT DETECTED
- MTB detected; RIF Resistance INDETERMINATE
- MTB NOT DETECTED.
- INVALID (the presence or absence of MTB cannot be determined)
- ERROR (the presence or absence of MTB cannot be determined)
- NO RESULT (the presence or absence of MTB cannot be determined

Xpert Ultra (Cepheid 2018)

- MTB (*M tuberculosis*) DETECTED HIGH; RIF (rifampicin) Resistance DETECTED
- MTB DETECTED MEDIUM; RIF Resistance DETECTED
- MTB DETECTED LOW; RIF Resistance DETECTED
- MTB DETECTED VERY LOW; RIF Resistance DETECTED
- MTB DETECTED HIGH; RIF Resistance NOT DETECTED
- MTB DETECTED MEDIUM; RIF Resistance NOT DETECTED
- MTB DETECTED LOW; RIF Resistance NOT DETECTED
- MTB DETECTED VERY LOW; RIF Resistance NOT DETECTED
- MTB DETECTED HIGH; RIF Resistance INDETERMINATE
- MTB DETECTED MEDIUM; RIF Resistance INDETERMINATE
- MTB DETECTED LOW; RIF Resistance INDETERMINATE
- MTB DETECTED VERY LOW; RIF Resistance INDETERMINATE
- MTB Trace DETECTED; RIF Resistance INDETERMINATE
- INVALID (the presence or absence of MTB cannot be determined)
- ERROR (the presence or absence of MTB cannot be determined)
- NO RESULT (the presence or absence of MTB cannot be determined)

Xpert Ultra incorporates a semi-quantitative classification for results. MTB Trace DETECTED corresponds to the lowest bacterial burden for detection of *M tuberculosis* (Chakravorty 2017). We considered a trace result to mean MTB (*M tuberculosis*) DETECTED.

However, no rifampicin-resistance results were available for participants with trace results because for trace results, rifampicin resistance is always reported as INDETERMINATE (Cepheid 2018).

Target conditions

The target conditions were active pulmonary tuberculosis and rifampicin resistance.

Reference standards

For tuberculosis, the reference standards were solid culture or automated liquid culture.

For rifampicin resistance, the reference standards were culture-based drug susceptibility testing (DST) and line probe assays (WHO LPA 2016). Acceptable methods for DST included the proportion method, performed on solid media, such as Lowenstein-Jensen, and use of a commercial liquid culture system, such as Mycobacteria Growth Indicator Tube (MGIT) 960 automated mycobacterial detection system (BD, USA).

Search methods for identification of studies

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

Electronic searches

We searched the following databases on 19 March 2020, without language restriction, using the search terms and strategy described in Appendix 1.

- Cochrane Infectious Diseases Specialized Register.
- MEDLINE (Pubmed, from 1966).
- Embase (OVID, from 1947).
- Science Citation Index - Expanded (from 1900), Conference Proceedings Citation Index - Science (CPCI-S, from 1990), Social Science Citation Index (from 1900), Conference Proceedings Citation Index- Social Science & Humanities(from 1990), all from the Web of Science.
- Scopus (Elsevier, from 1970).
- Latin American Caribbean Health Sciences Literature (LILACS; BIREME, https://lilacs.bvsalud.org/en/ from 1982).

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 (from 1990) for dissertations.

Searching other resources

We reviewed reference lists of included articles, related Cochrane Reviews (Horne 2019) 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 TB Programme, and other experts in the field of tuberculosis diagnostics for information on ongoing and unpublished studies.

Data collection and analysis

Selection of studies

We used Covidence to manage the selection of studies (Covidence). Two review authors independently and in parallel scrutinized titles and abstracts identified from literature searching to identify potentially eligible studies. We retrieved the article of any citation, identified by any review author, for full-text review. Two review authors independently and in parallel assessed articles for inclusion using the predefined selection criteria. We resolved any discrepancies by discussion or with a third review author. We recorded all studies excluded after full-text assessment, along with our reasons for their exclusion in the Characteristics of excluded studies table, and illustrated the study selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

We extracted data on the following characteristics.

- Author, publication year, study design, country where study was located, clinical setting.
- Population characteristics: age, sex, AFB smear status, HIV status.
- Index test(s), Xpert MTB/RIF or Xpert Ultra.
- Reference standard.
- Quality Assessment of Studies of Diagnostic Accuracy - Revised (QUADAS-2) items (Whiting 2011).
- Number of TP, FP, FN, and TN (i.e. true positives, false positives, false negatives, and true negatives) and trace results, with respect to culture.
- Number of uninterpretable results for detection of pulmonary tuberculosis.
- Number of indeterminate results for detection of rifampicin resistance.

We classified country income status as either low- and 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, TB/HIV, or MDR-TB, according to the classification by the WHO (WHO Global TB Report 2019).

We followed Cochrane policy, which states that "authors of primary studies will not extract data from their own study or studies. Instead, another author will extract these data, and check the interpretation against the study report and any available study registration details or protocol".

Assessment of methodological quality

We used the QUADAS-2 tool, tailored to this review, to assess the quality of the included studies (Whiting 2011; Appendix 2). 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. We presented the results of this quality assessment in text, tables, and graphs.

Statistical analysis and data synthesis

We performed descriptive analyses for the results of the included studies using Stata 15 (Stata). We determined sensitivity and

specificity estimates and 95% confidence intervals (CIs) for individual studies and generated forest plots using Review Manager 5 (Review Manager 2020).

When possible, we carried out meta-analyses to estimate the pooled sensitivity and specificity of the index tests separately for tuberculosis detection and rifampicin resistance detection. We determined the pooled accuracy estimates using an adaptation of the bivariate random-effects model of Reitsma 2005, which uses the exact binomial likelihood for the observed proportions (Chu 2006). The bivariate random-effects approach allows us to calculate the pooled estimates of sensitivity and specificity while accounting for:

1. variation in sensitivity and specificity estimates within individual studies;
2. correlation between sensitivity and specificity across studies; and
3. variation in sensitivity and specificity between studies.

In addition, we determined positive and negative predictive values at pretest probabilities (0.5% and 5%) suggested by the WHO.

For analysis of Xpert MTB/RIF or Xpert Ultra accuracy for detection of rifampicin resistance, we included participants who:

1. were culture-positive;
2. had a valid phenotypic drug susceptibility test (DST) or line probe assay (LPA) result;
3. were Xpert MTB/RIF or Xpert Ultra tuberculosis-positive; and
4. had a valid Xpert MTB/RIF or Xpert Ultra result for rifampicin resistance, detected or not detected (susceptible).

Sensitivity = Xpert MTB/RIF (or Xpert Ultra) rifampicin resistance detected/phenotypic DST or LPA rifampicin-resistant

Specificity = Xpert MTB/RIF (or Xpert Ultra) rifampicin resistance not detected/phenotypic DST or LPA rifampicin-susceptible

We estimated all models using a Bayesian approach, with low-information prior distributions, using OpenBUGS software (Version 3.2.3; Lunn 2009), along with R (Version 3.3.2; R Core Team 2019). Under the Bayesian approach, all unknown parameters must be provided a prior distribution that defines the range of possible values of the parameter and the likelihood of each of those values based on information external to the data. In order to let the observed data determine the final results, we chose to use low-information prior distributions over the pooled sensitivity and specificity parameters and their between-study standard deviation parameters.

Meta-analysis models can be sensitive to the choice of prior distributions over between-study standard deviation parameters. We therefore carried out sensitivity analyses and considered alternative prior distributions that are less informative, allowing a wider range of possible values. We included information from the prior distribution in combination with the observed data in accordance with Bayes' theorem to obtain a posterior distribution for each unknown parameter.

Using a sample from the posterior distribution, we can obtain various descriptive statistics of interest. We estimated the median pooled sensitivity and specificity and their 95% credible intervals (CrIs). The median or the 50% quantile is the value below which lies 50% of the posterior sample. We reported the median because the posterior distributions of some parameters may be skewed and the median would be considered a better point estimate of the unknown parameter than the mean in such cases. The 95% CrI is the Bayesian equivalent of the classical (frequentist) 95% CI. (We indicated 95% CI for individual study estimates and 95% CrI for pooled study estimates, as appropriate.) The 95% CrI may be interpreted as an interval that has a 95% probability of capturing the true value of the unknown parameter, given the observed data and the prior information. We generated bivariate plots of the credible and prediction regions in the receiver operating characteristic (ROC) space using R (version 3.3.2; R Core Team 2019).

We found only one study that compared the accuracy of Xpert MTB/RIF and Xpert Ultra in a single high-risk group and setting, thus we analysed the accuracy estimates descriptively in text, tables, and forest plots.

Approach to uninterpretable index test results

The index tests report an uninterpretable test result for unexpected results with any of the internal control measures of the assay.

In previous reviews, we found very few uninterpretable results reported, as was the case here, and chose to exclude them from the bivariate meta-analyses (Horne 2019).

Investigations of heterogeneity

We visually inspected forest plots and the summary receiver operating characteristic (SROC) plots for heterogeneity. We set out to investigate a number of potential sources of heterogeneity, described below using subgroup analyses; however, our ability to investigate these sources was limited by the available data. We added percentage of participants with tuberculosis symptoms as a continuous covariate on forest plots and visually inspected the plots. We intended to perform subgroup analyses among studies conducted in high versus not high tuberculosis burden countries, and similarly for high TB/HIV burden and high MDR-TB burden versus not high-burden countries. However, most studies were conducted in high-burden countries (Differences between protocol and review).

Sensitivity analyses

We intended to perform sensitivity analyses by limiting inclusion in the meta-analyses according to the following criteria:

- studies that explicitly represented the use of the index tests for the screening of individuals irrespective of signs and symptoms of tuberculosis;
- studies that used liquid culture as the reference standard;
- studies where a consecutive or random sample of participants were enrolled. We planned to exclude studies where we answered no or unclear to the QUADAS-2 patient selection signalling question: "Could the selection of patients have introduced bias?"

However, we did not perform any sensitivity analyses because all studies met these criteria (Differences between protocol and review).

Assessment of reporting bias

We did not formally assess reporting bias using funnel plots or regression tests as these have not been reported as helpful for diagnostic test accuracy studies (Macaskill 2010).

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Balshem 2011; Schünemann 2008; Schünemann 2016), and GRADEpro GDT 2020 software. In the context of a systematic review, ratings of the certainty of the evidence reflect the extent of our confidence that the estimates of effect (including test accuracy and associations) are correct. As recommended, we rated the certainty of the evidence as either high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) for five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias.

For each outcome, we considered the certainty of the evidence to begin as high when high-quality observational studies (cross-sectional or cohort studies) enrolled participants with diagnostic uncertainty. If we had a reason for downgrading, we used our judgement to classify the reason as serious (downgraded by one level) or very serious (downgraded by two levels). We summarized this information in the 'Summary of findings' tables.

As recommended, we applied GRADE in the following ways (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, interventions, and outcomes (accuracy measures). For example, we noted whether the population was the same in the studies compared to the question asked. We also used prevalence as a guide to whether there was indirectness in the population.
- Inconsistency: GRADE recommends downgrading for unexplained inconsistency in sensitivity and specificity estimates. We carried out prespecified analyses and downgraded only when we could not explain inconsistency in the accuracy estimates.
- Imprecision: we considered a precise estimate to be one that would allow a clinically meaningful decision. We considered the width of the CrI and ask ourselves, 'Would we make a different decision if the lower or upper boundary of the CrI represented the truth?' In addition, we determined projected ranges for true positives (TP), false negatives (FN), true negatives (TN), and false positives (FP) for a given prevalence of tuberculosis and make judgements on imprecision from these calculations.
- 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 are not published.

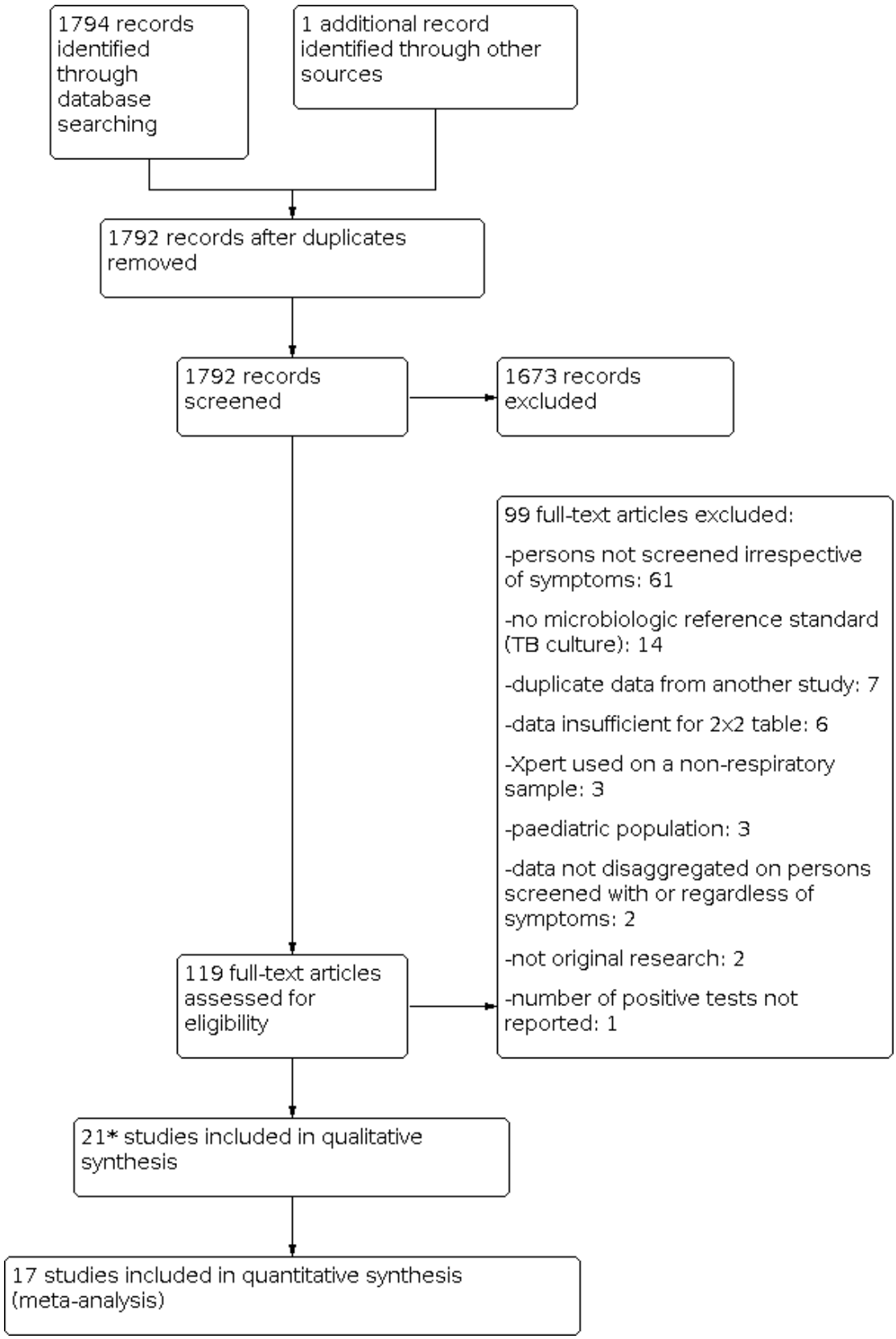
RESULTS

Results of the search

We identified 1794 records through database searching and one additional record through other sources. After duplicate removal, we screened a total of 1792 citations by title and abstract for inclusion. Of these, we assessed 119 full-text publications against our inclusion criteria and excluded 99 publications. Exclusions were mainly due to persons not screened irrespective of symptoms (n = 61), no microbiologic reference standard (n = 14), duplicate data from another study (n = 7), and data insufficient for the 2x2 table (n = 6). Other reasons for exclusion included Xpert MTB/RIF used on a non-respiratory specimen (n = 3), paediatric population (n = 3), data not disaggregated on persons screened with or regardless of symptoms (n = 2), not original research (n = 2), and number of positive tests not reported (n = 1).

Thus we identified 20 publications, which included 21 unique studies (one publication contributed two distinct cohorts). (Al-Darraji 2013; Al-Darraji 2016; Balcha 2014; Beyanga 2018; Bjerrum 2016; Dorman 2012; Heidebrecht 2016; Henostroza 2016; Kempker 2019; LaCourse 2016; Lawn 2011; Lawn 2012; Lopez-Varela 2019; Mollel 2017; Ntinginya 2012; O'Grady 2012; Reeve 2019a; Reeve 2019b; Santos 2020; Tahseen 2018; Yoon 2017). Of the total 21 studies, 18 studies provided data for the detection of pulmonary tuberculosis using Xpert MTB/RIF and one study provided data for both Xpert MTB/RIF and Xpert Ultra (Reeve 2019b). Three studies provided data for detection of rifampicin resistance (Al-Darraji 2013; Lawn 2011; O'Grady 2012). All included studies used a cross-sectional study design. We did not identify any studies that conducted general population-wide screening for tuberculosis (e.g. national prevalence surveys) that met inclusion criteria for this review. Figure 2 shows the flow of studies in the review. We recorded the excluded studies and the reasons for their exclusion in the Characteristics of excluded studies table.

Figure 2. Study flow diagram, PRISMA. *One publication, Reeve 2019, contributed two distinct studies, which were classified as Reeve 2019a and Reeve 2019b.



Methodological quality of included studies

Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis

Figure 3 and Figure 4 summarize risk of bias and applicability concerns for studies evaluating Xpert MTB/RIF (n = 20) and Xpert Ultra (n = 1) as screening tests for pulmonary tuberculosis.

Figure 3. Risk of bias and applicability concerns graph for Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis: review authors' judgements about each domain presented as percentages across included studies.

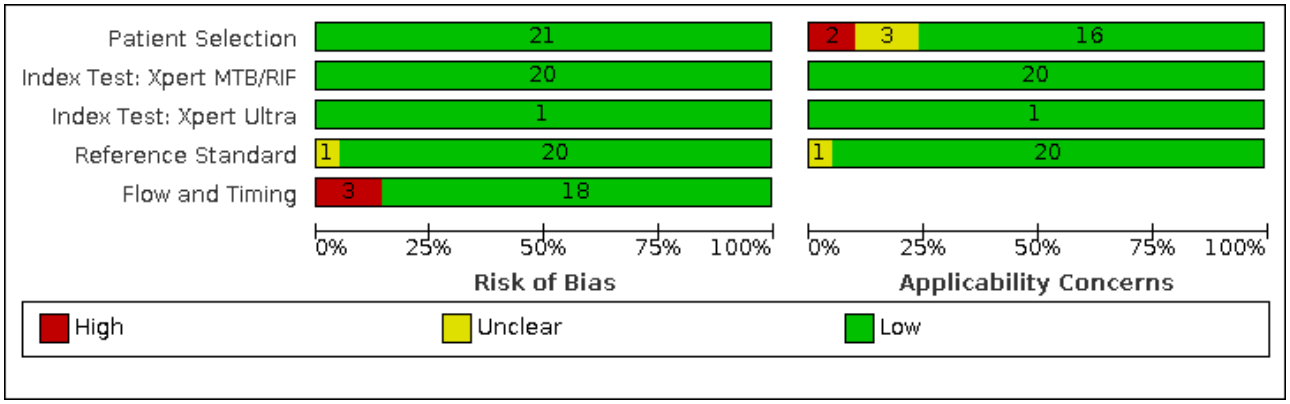


Figure 4. Risk of bias and applicability concerns summary for Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis: review authors' judgements about each domain for each included study.

In the patient selection domain, we considered all studies to have low risk of bias because the studies enrolled a consecutive or random sample of eligible adult participants and avoided inappropriate exclusions. Regarding applicability (Patient Selection domain), we considered 16 studies (76%) to have low concern because the study population resembled a population that was selected for tuberculosis screening in community settings or primary care centres. We considered two studies (10%) to have high concern because participants were evaluated exclusively as inpatients in tertiary care centres (Heidebrecht 2016; O'Grady 2012), and three studies (14%) to have unclear concern, two studies because they enrolled a small proportion of people younger than 15 years old (Beyanga 2018; Ntinginya 2012), and one study because 2% of the enrolled population had received tuberculosis treatment for up to two weeks (Balcha 2014).

In the index test domain, we considered all studies to have low risk of bias because the results of the index tests (Xpert MTB/RIF and Xpert Ultra) are automatically generated, the user is provided with printable test results, and the positivity threshold is prespecified. Regarding applicability (Index Test domain), we considered all studies to have low concern.

In the reference standard domain, we considered 20 studies (95%) to have low risk of bias. We considered one study to have unclear risk of bias because information about blinding was not reported (Mollel 2017). Regarding applicability (Reference Standard domain), we considered 20 studies (95%) to have low concern because these studies performed a test to identify *M tuberculosis* species (speciation) and one study to have unclear concern because information about speciation was not reported (Mollel 2017).

In the flow and timing domain, we considered 18 studies (86%) to have low risk of bias because all participants were included in the analysis. We considered three studies to have high risk of bias because not all enrolled participants were included in the analysis (Heidebrecht 2016; Ntinginya 2012; Santos 2020).

Xpert MTB/RIF and Xpert Ultra as screening tests for rifampicin resistance

Figure 5 and Figure 6 show risk of bias and applicability concerns for studies evaluating Xpert MTB/RIF (n = 3) as screening tests for rifampicin resistance.

Figure 5. Risk of bias and applicability concerns graph for Xpert MTB/RIF as a screening test for rifampicin resistance: review authors' judgements about each domain presented as percentages across included studies.

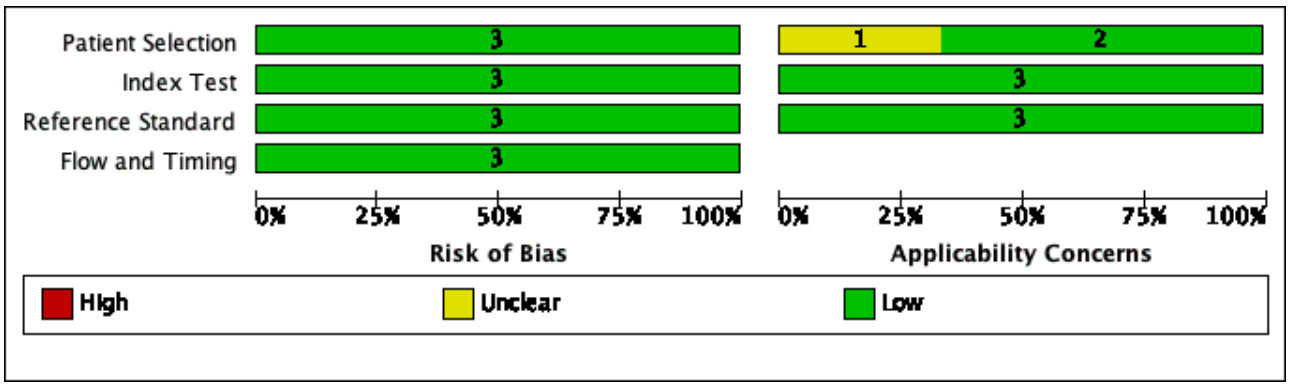
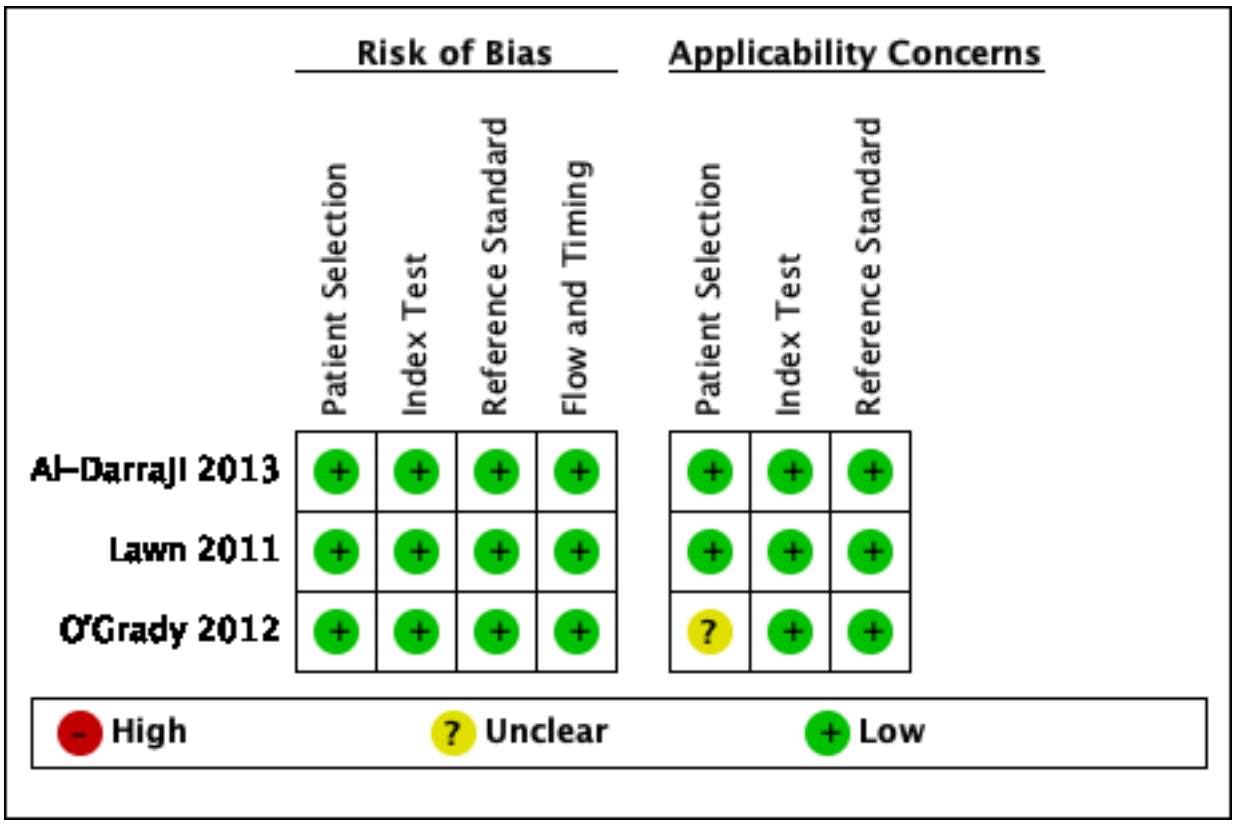


Figure 6. Risk of bias and applicability concerns summary for Xpert MTB/RIF as a screening test for rifampicin resistance: review authors' judgements about each domain for each included study.



Regarding risk of bias, for the four domains (patient selection, index test, reference standard, and flow and timing), we considered all three studies (100%) to at low risk (Al-Darraji 2013; Lawn 2011; O'Grady 2012). Regarding applicability, in the Patient Selection domain, we considered two studies (67%) to have low concern about applicability (Al-Darraji 2013; Lawn 2011), and one study to have unclear concern because participants were evaluated exclusively as inpatients in a tertiary care centre (O'Grady 2012).

Findings

The median study population size of the included studies was 442 (Interquartile range (IQR) 114 to 624). Fifteen studies (75%) were conducted in high tuberculosis burden and 16 (80%) in high TB/HIV-burden countries. We presented key characteristics of the included studies in the Characteristics of included studies table. Twelve (60%) studies were performed in people living with HIV. Of the total 21 studies, none evaluated the tests for screening in the general population.

Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis

Xpert MTB/RIF as a screening test in people living with HIV, irrespective of tuberculosis symptoms

Twelve studies evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis in people living with HIV (Al-Darraji 2013; Balcha 2014; Bjerrum 2016; Henostroza 2016; Kempker 2019; LaCourse 2016; Lawn 2012; Lopez-Varela 2019; Mollel 2017; Reeve 2019a; Tahseen 2018; Yoon 2017). Xpert MTB/RIF sensitivity estimates varied from 43% to 100%. The lowest sensitivity was reported by LaCourse 2016, a study notable for enrolling HIV-positive women accessing prevention of mother-to-child transmission services as part of antenatal care. Specificity varied less than sensitivity, from 92% to 100%, Figure 7. Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 61.8% (53.6 to 69.9) and 98.8% (98.0 to 99.4), (12 studies, 4775 participants, 602 (12.6%) with tuberculosis), Table 1, Figure 8.

Figure 7. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in people living with HIV by percentage of tuberculosis symptoms. The individual studies are ordered by decreasing percentage of participants with tuberculosis symptoms. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative.

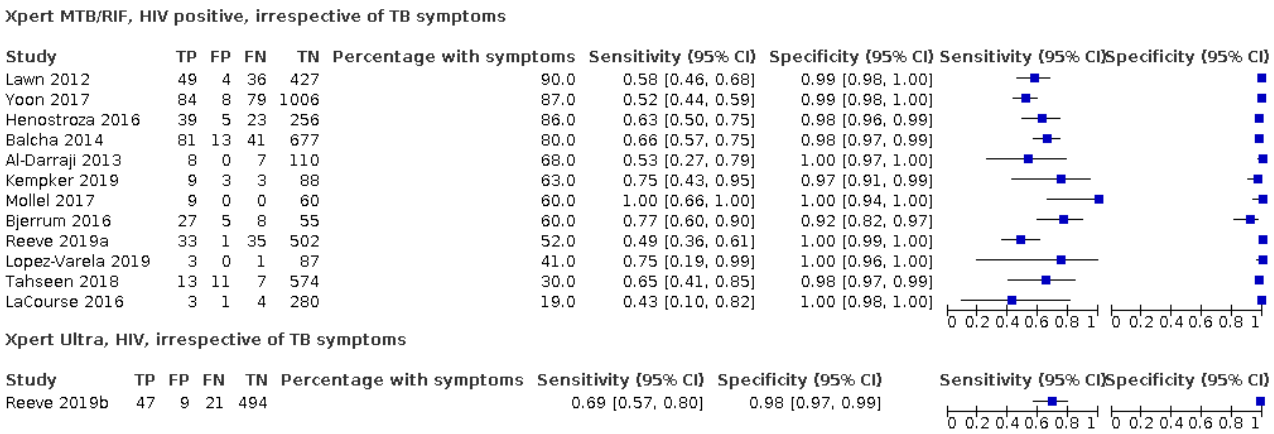
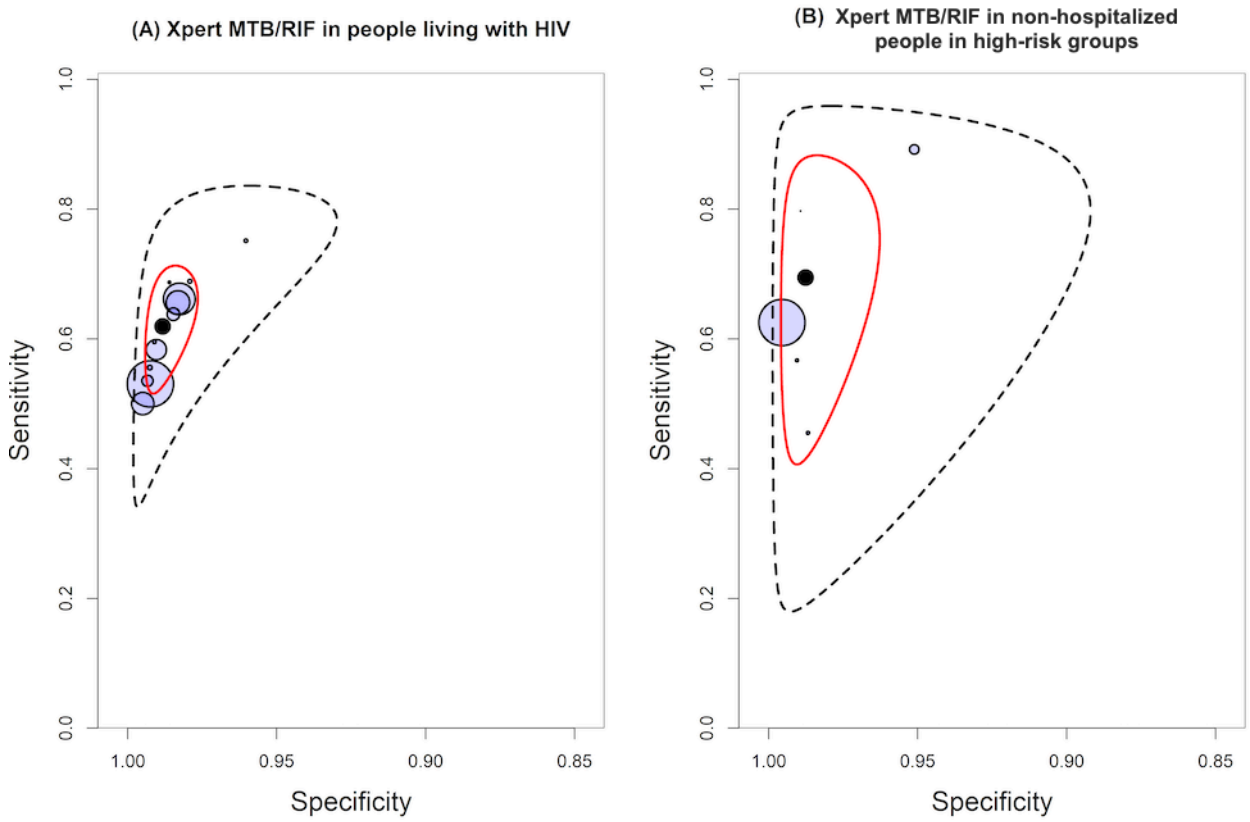


Figure 8. Summary plots of the accuracy of Xpert MTB/RIF as a screening test for pulmonary tuberculosis in (A) people living with HIV and (B) non-hospitalized people in high-risk groups. Each individual study is represented by a shaded circle. The size of the circle is proportional to the sample size of the study such that larger studies are represented by larger circles. The filled circle is the median pooled estimate for sensitivity and specificity. The solid lines represent the 95% credible region around the summary estimate; the dashed lines represent the 95% prediction region. The range is truncated to consider only those regions of the ROC space where data have been observed.



Investigations of heterogeneity

Xpert MTB/RIF as a screening test in people living with HIV, by percentage of participants with tuberculosis symptoms

In HIV-positive populations where 50% or more had tuberculosis symptoms, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 62.9% (53.9 to 72.1) and 98.7% (97.7 to 99.4), (9 studies, 3791 participants, 571 (15.1%) with tuberculosis).

In HIV-positive populations where less than 50% had tuberculosis symptoms, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 61.1% (35.5 to 82.3) and 99.1% (97.6 to 99.8), (3 studies, 984 participants, 31 (3.2%) with tuberculosis).

Confidence intervals for sensitivity and specificity estimates in the two subgroups overlapped, indicating no significant differences in accuracy based on tuberculosis symptoms, Table 1, Figure 7.

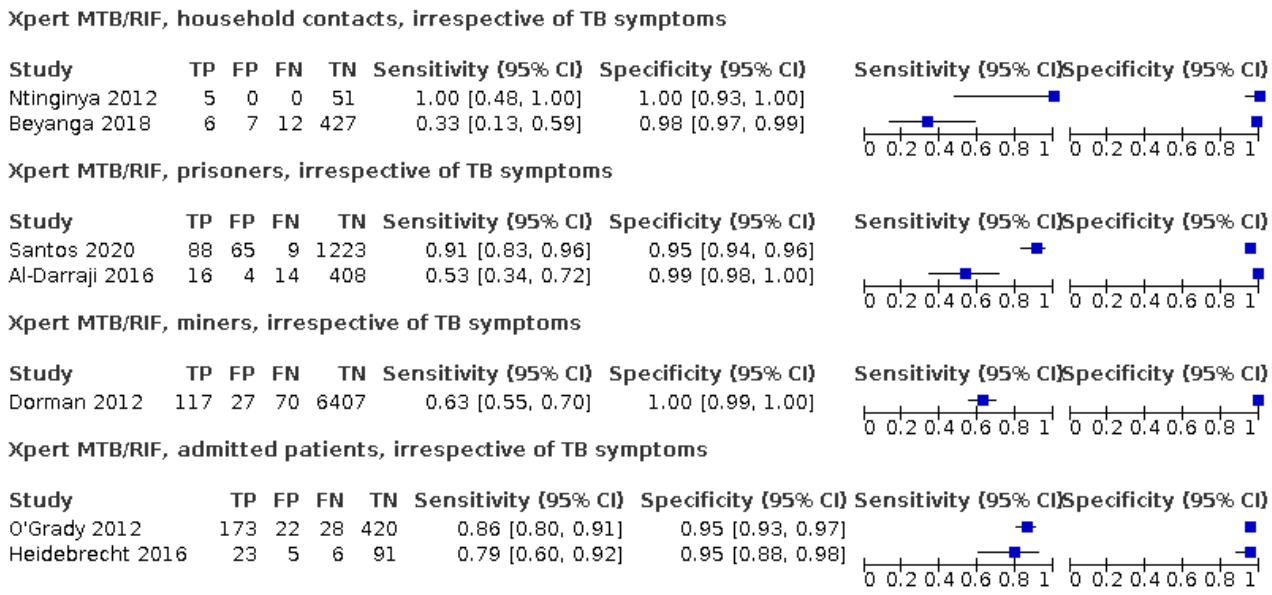
Xpert Ultra as a screening test in people living with HIV, irrespective of tuberculosis symptoms

One study evaluated Xpert Ultra as a screening test for pulmonary tuberculosis (Reeve 2019b). Xpert Ultra sensitivity and specificity (95% CI) were 69% (57 to 80) and 98% (97 to 99), Figure 7.

Xpert MTB/RIF as a screening test in household contacts, irrespective of tuberculosis symptoms

Two studies evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis in household contacts. Xpert MTB/RIF sensitivity and specificity (95% CI) were 33% (13 to 59) and 98% (97 to 99) (Beyanga 2018) and 100% (48 to 100) and 100% (93 to 100) (Ntinginya 2012), Figure 9.

Figure 9. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in household contacts, people in prison, miners, and people admitted to hospital, irrespective of tuberculosis symptoms. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative.



Xpert MTB/RIF as a screening test in people residing in prisons, irrespective of tuberculosis symptoms

Two studies evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis in persons residing in prisons. Xpert MTB/RIF sensitivity and specificity (95% CI) were 53% (34 to 72) and 99% (98 to 100) (Al-Darraji 2016) and 91% (83 to 96) and 95% (94 to 96) (Santos 2020), Figure 9.

Xpert MTB/RIF as a screening test in miners, irrespective of tuberculosis symptoms

One study evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis in miners (Dorman 2012). Xpert MTB/RIF sensitivity and specificity (95% CI) were 63% (55 to 70) and 100% (99 to 100), Figure 9.

Xpert MTB/RIF as a screening test in non-hospitalized people in high-risk groups combined, irrespective of tuberculosis symptoms

We estimated pooled sensitivity and specificity including the five studies that evaluated Xpert MTB/RIF in household contacts, miners, and people residing in prisons (i.e. populations that did not exclusively include people living with HIV and inpatient settings) (Al-Darraji 2016; Beyanga 2018; Dorman 2012; Ntinginya 2012; Santos 2020). Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 69.4% (47.7 to 86.2) and 98.8% (97.2 to 99.5), (5 studies, 8956 participants, 337 (3.8%) with tuberculosis), Table 1, Figure 8.

Xpert MTB/RIF as a screening test in patients admitted to the hospital, irrespective of tuberculosis symptoms

Two studies evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis in persons admitted to the hospital. Xpert MTB/RIF sensitivity and specificity (95% CI) were 79% (60 to 92) and 95% (88 to 98) (Heidebrecht 2016) and 86% (80 to 91) and 95% (93 to 97) (O'Grady 2012), Figure 9. In Heidebrecht 2016, 62% of patients had HIV and in O'Grady 2012, 71% of patients had HIV.

Xpert MTB/RIF and Xpert Ultra as a screening test in the general population, irrespective of tuberculosis symptoms

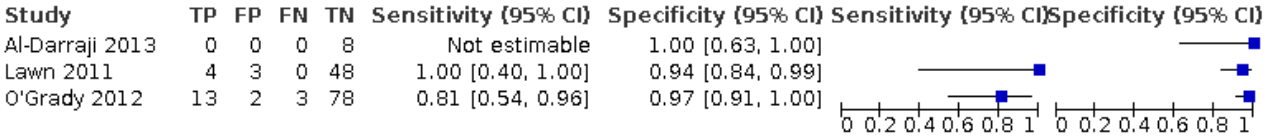
We did not identify any studies that evaluated Xpert MTB/RIF or Xpert Ultra as a screening test in general populations, irrespective of signs or symptoms of tuberculosis.

Xpert MTB/RIF and Xpert Ultra as screening tests for rifampicin resistance

Xpert MTB/RIF as a screening test for rifampicin resistance

Three studies evaluated Xpert MTB/RIF as a screening test for rifampicin resistance (Al-Darraji 2013; Lawn 2011; O'Grady 2012). One study reported zero rifampicin-resistant results and hence, sensitivity was not estimable (Al-Darraji 2013). Sensitivity (95% CI) was 100% (40 to 100) in Lawn 2011 and 81% (54 to 96) in O'Grady 2012; specificity ranged from 94% to 100%, Figure 10.

Figure 10. Forest plots of Xpert MTB/RIF sensitivity and specificity for rifampicin resistance, in people irrespective of tuberculosis symptoms. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative.



Xpert Ultra as a screening test for rifampicin resistance

We did not identify any studies that evaluated Xpert Ultra as a screening test for detection of rifampicin resistance.

DISCUSSION

Summary of main results

This Cochrane Review summarizes the current literature on the accuracy of Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis and rifampicin resistance in adults, irrespective of signs and symptoms of tuberculosis. We identified 21 studies: 18 studies (13,114 participants) evaluated Xpert MTB/RIF as a screening test for pulmonary tuberculosis and one study (571 participants) evaluated both Xpert MTB/RIF and Xpert Ultra. Three studies (159 participants) evaluated Xpert MTB/RIF for rifampicin resistance.

- As a screening test for pulmonary tuberculosis in people living with HIV, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 61.8% (53.6 to 69.9) and 98.8% (98.0 to 99.4), Summary of findings 1.
- As a screening test for pulmonary tuberculosis in people living with HIV (one study), Xpert Ultra sensitivity and specificity (95% CI) were 69% (57 to 80) and 98% (97 to 99), Summary of findings 1.
- As a screening test for pulmonary tuberculosis in non-hospitalized people in high-risk groups, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 69.4% (47.7 to 86.2) and 98.8% (97.2 to 99.5), Summary of findings 1.
- As a screening test for rifampicin resistance, Xpert MTB/RIF sensitivity was 81% and 100%, and specificity was 94% to 100%, Summary of findings 2.

Xpert MTB/RIF as a screening test for pulmonary tuberculosis in people living with HIV

Results of these studies indicate that, in theory, for a population of 1000 people where 50 have tuberculosis on culture, 40 would be Xpert MTB/RIF-positive; of these, 9 (22%) would not have tuberculosis (false-positives); and 960 would be Xpert MTB/RIF-negative; of these, 19 (2%) would have tuberculosis (false-negatives), Summary of findings 1.

Xpert Ultra as a screening test for pulmonary tuberculosis in people living with HIV

Results of these studies indicate that, in theory, for a population of 1000 people where 50 have tuberculosis on culture, 53 would be Xpert Ultra-positive; of these, 19 (36%) would not have tuberculosis (false-positives); and 947 would be Xpert Ultra-negative; of these, 16 (2%) would have tuberculosis (false-negatives), Summary of findings 1.

Xpert MTB/RIF as a screening test for pulmonary tuberculosis in non-hospitalized people in high-risk groups

Results of these studies indicate that, in theory, for a population of 1000 people where 10 have tuberculosis on culture, 19 would be Xpert MTB/RIF-positive; of these, 12 (63%) would not have tuberculosis (false-positives); and 981 would be Xpert MTB/RIF-negative; of these, 3 (0%) would have tuberculosis (false-negatives), Summary of findings 1.

Xpert MTB/RIF and Xpert Ultra as a screening test for pulmonary tuberculosis in high-risk groups

Our review found that Xpert MTB/RIF and Xpert Ultra, when used as a screening test for tuberculosis, successfully identified tuberculosis in people who were screened, regardless of symptoms of pulmonary tuberculosis in high-risk groups and persons attending health facilities for reasons other than diagnosis of tuberculosis.

The sensitivity and specificity of Xpert MTB/RIF and Xpert Ultra, compared to the microbiological reference standard of tuberculosis culture, was similar in people living with HIV and other high-risk groups, when used to screen for tuberculosis, irrespective of the presence of signs and symptoms.

Current WHO and national guidelines recommend screening people living with HIV for tuberculosis symptoms and reserve diagnostic testing for people with symptoms. In this review, we evaluated two subgroups of studies of people living with HIV: studies in which 50% or more participants had tuberculosis symptoms, and studies in which less than 50% of participants had tuberculosis symptoms. While we did not identify any studies using Xpert MTB/RIF to screen entirely asymptomatic people living with HIV for tuberculosis, and are thus unable to estimate Xpert MTB/RIF accuracy in people living with HIV without symptoms, evidence from the subgroup analysis suggests that there is little difference in the accuracy of the Xpert test in heavily symptomatic versus less symptomatic populations of people living with HIV. The observed prevalence of pulmonary tuberculosis was substantially higher in the high symptom prevalence subgroup of studies compared to the low symptom prevalence subgroup of studies (15.1% versus 3.2%), but the sensitivity and specificity of Xpert MTB/RIF were not meaningfully different in each subgroup.

We recognize that patient-important outcomes including the effect of the use of Xpert MTB/RIF and Xpert Ultra for screening on treatment initiation, cure, mortality, and community incidence are important to patients, clinicians, and decision-makers. However,

evaluating such outcomes would have required a different methodology than this study, which focused on test accuracy in the application of screening irrespective of symptoms. We did not identify any studies that assessed both accuracy with a tuberculosis culture reference standard and people-important outcomes. The ACT3 study in Viet Nam (Marks 2019) was a community-randomized trial evaluating the effect of screening for tuberculosis using Xpert MTB/RIF in adults 15 years and older, irrespective of signs and symptoms of tuberculosis, on the prevalence of tuberculosis. Tuberculosis culture was performed on specimens testing positive by Xpert MTB/RIF. The study found 94 positive Xpert MTB/RIF results among 41,680 adults tested in the control arm; tuberculosis culture was positive in 49 of the positive Xpert MTB/RIF results for a positive predictive value of 52%. In the intervention communities of 42,150 adults, only 53 cases were detected by Xpert MTB/RIF (33 culture-positive), a significant reduction in tuberculosis prevalence. Though we were unable to include this study in our review, as the reference microbiological standard (tuberculosis culture) was not systematically performed with every Xpert MTB/RIF test, the ACT3 study is an important contribution to the evidence on use of Xpert MTB/RIF in population-based screening and the effect on patient-important outcomes.

There is increasing interest in using Xpert MTB/RIF and Xpert Ultra for population-based screening for tuberculosis, such as for national prevalence surveys. Recent national tuberculosis prevalence surveys including in Vietnam (Nguyen 2020), Kenya (Enos 2018), and Bangladesh (WHO Consolidated Guidelines (Module 3) 2020) employed screening strategies with Xpert MTB/RIF or Xpert Ultra and reference testing with mycobacterial culture; prevalence surveys in South Africa, Zambia, and Myanmar employed Xpert Ultra and culture for reference testing (WHO Consolidated Guidelines (Module 3) 2020) . However, all prevalence surveys we identified employed Xpert MTB testing only for persons with radiographic signs and/or symptoms of tuberculosis, thus we were unable to determine the screening accuracy of these molecular tests in general population screening in persons irrespective of signs and symptoms of tuberculosis. This is an important limitation of the review.

Decisions of how and where to implement Xpert MTB/RIF and Xpert Ultra for tuberculosis screening in persons irrespective of symptoms require, in addition to concerns of test accuracy as reviewed here, careful consideration of resource utilization requirements and cost-effectiveness of these tests, which are highly dependent on the setting, population, and underlying prevalence of tuberculosis in the population. While there are substantial data supporting the cost-effectiveness for use of Xpert MTB/RIF and Xpert Ultra as an initial diagnostic test in symptomatic individuals presenting to a healthcare facility in high-burden settings (WHO 2016), there is scarce published evidence for cost-effectiveness of these tests when used for screening people irrespective of signs and symptoms of tuberculosis. Communities and populations differ in how they can access rapid molecular diagnostic tests for tuberculosis: when provided in a centralized fashion in a healthcare or other facility-based setting (e.g. primary care clinics providing services to people living with HIV, inpatient hospital facilities, prison facilities, large mining complexes), fewer resources are needed to bring the tests in proximity to people being screened. Screening becomes much more resource-intensive when delivered in decentralized, community-based or household contact-tracing settings, but conversely these settings may be where the majority of undetected tuberculosis cases may be found, and consequently the impact on community transmission the highest.

Strengths and weaknesses of the review

Completeness of evidence

The findings in this review are based on comprehensive searching, strict selection criteria, and standardized data extraction. We corresponded with study authors to obtain additional data and information that was missing from the papers. The search strategy included studies published in all languages. We acknowledge that we may have missed studies despite the comprehensive search; however, we think it unlikely that the findings would have changed.

Accuracy of the reference standards used

Culture is regarded as the best available reference standard for the bacteriological confirmation of pulmonary tuberculosis and was the reference standard for tuberculosis in this review. Liquid culture is considered to be more sensitive than solid culture (Lewinsohn 2017). In this review 17 (85%) studies used liquid culture as the reference standard.

Quality and quality of reporting of the included studies

All studies used consecutive or random selection of participants and interpreted the reference standard results without knowledge of index test results. Xpert results are generated automatically, without requiring operator interpretation. Studies were generally well reported, although we corresponded with several authors for missing information.

Applicability of findings to the review question

For screening for pulmonary tuberculosis, we had low concern for applicability because in most studies, participants represented a population that was selected for tuberculosis screening in community settings or primary care centres. Fifteen studies (75%) were conducted in high tuberculosis burden settings and hence the results may not be applicable to other settings. We only identified one study that evaluated Xpert Ultra and were therefore unable to compare test accuracy with that of Xpert MTB/RIF, a secondary objective of the review. The one study of Xpert Ultra was conducted in people living with HIV in South Africa, hence applicability to other settings comes with some uncertainty.

For screening for detection of rifampicin resistance detection, of the three included studies we were unclear about the applicability of one study (33%) because this study evaluated the test in adult medical inpatients at a tertiary hospital, rather than a community setting or primary care centre.

We did not identify any studies that screened other groups at high risk for tuberculosis that met inclusion criteria for this review, which included the concomitant use of culture as a reference standard. These populations include people experiencing homelessness, people with diabetes mellitus, people who abuse alcohol, people who smoke, and healthcare workers. We did not identify any studies that conducted general population-wide screening for tuberculosis (e.g. national prevalence surveys) that met inclusion criteria for this review. This is an important limitation of the review.

AUTHORS' CONCLUSIONS

Implications for practice

Of the high-risk groups evaluated, Xpert MTB/RIF applied as a screening test was accurate for tuberculosis in high tuberculosis burden settings. Sensitivity and specificity were similar in people living with HIV and non-hospitalized people in high-risk groups. In people living with HIV, Xpert Ultra sensitivity was slightly higher than that of Xpert MTB/RIF and specificity similar. As there was only one study of Xpert Ultra in this analysis, results should be interpreted with caution. There were no studies that evaluated the tests in people with diabetes mellitus and other groups considered at high risk for tuberculosis, or in the general population.

Implications for research

Several high-risk groups were considered that were not represented in any studies in this review, but evidence of the performance of Xpert MTB/RIF, Xpert Ultra, and other rapid molecular tests will be important to inform their use as screening tests for tuberculosis. In particular, priority populations for research are those in whom signs and symptoms of tuberculosis are less sensitive for tuberculosis or in whom the consequences of a missed diagnosis of tuberculosis are particularly severe, such as pregnant women, people with diabetes mellitus, and people who smoke tobacco. Only one study using Xpert Ultra (in people living with HIV) contributed evidence to this review, and additional studies of the accuracy of Xpert Ultra measured against tuberculosis culture in screening people irrespective of symptoms, with particular attention to false-positives, are needed to understand the implications of Xpert Ultra as a screening test. Operational research is needed to optimise the implementation of these tests for use in community settings, ensuring appropriate allocation of resources to enable test delivery, and to understand how use of the tests for screening affects the clinically meaningful outcomes of tuberculosis treatment initiation and cure, and effects on local epidemiology. If data are available, future reviews should assess the accuracy of a class of technologies, rather than a test from a single manufacturer.

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CHARACTERISTICS OF STUDIES

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

Al-Darraji 2013

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: not reported; HIV-positive prisoners were screened

Al-Darraji 2013 *(Continued)*

	Age: mean 37 years (standard deviation (SD) 6.6) Sex, female: 10% HIV infection: 100% History of TB: 29% Sample size: 125 Clinical setting: outpatient, point of care Laboratory level: other, prison Country: Malaysia World Bank Income Classification: middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: no Prevalence of TB cases in the study: 12.0%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 Speciation: yes Target condition: rifampicin resistance Reference standard for rifampicin resistance: MGIT 960, MTBDR-*plus* for confirmation
Flow and timing	
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

Al-Darraji 2013 *(Continued)*

DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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	

Al-Darraji 2016

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: prisoners were screened irrespective of s/sx; 59% reported at least 1 WHO sx Age: all >=18; mean age 36.4, SD 9.8 years Sex, female: 19% HIV infection: 29%

Al-Darraji 2016 *(Continued)*

	History of TB: 12% Sample size: 442 Clinical setting: outpatient, prison, point of care Laboratory level: other, prison Country: Malaysia World Bank Income Classification: middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: no Prevalence of TB cases in the study: 6.8%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 Speciation: yes
Flow and timing	
Comparative	
Notes	4 patients with Xpert MTB/RIF+ results had neg culture results, categorized as TB cases based on clinical & CXR findings

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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		

Al-Darraji 2016 *(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 2: Index Test (Xpert Ultra)			
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	

Balcha 2014

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-positive people screened for TB irrespective of symptoms Age: 18 years and older, median 32 years (IQR 28 to 40) Sex, female: 59% HIV infection: 100% History of TB: 6% Sample size: 810 Clinical setting: outpatient Laboratory level: intermediate Country: Ethiopia

Balcha 2014 *(Continued)*

	World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 15.0%
Index tests	Index: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 Speciation: yes
Flow and timing	
Comparative	
Notes	2% of participants were on anti-TB treatment for up to 2 weeks - risk of bias for participant selection

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			

Balcha 2014 *(Continued)*

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	

Beyanga 2018

Study characteristics	
Patient Sampling	Cross-sectional, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: participants were contacts of 93 pulmonary TB patients, irrespective of symptoms Age: all ages, median 22 years (IQR 15 to 37) Sex, female: 57% HIV infection: unknown History of TB: not reported Sample size: 456 Clinical setting: outpatient Laboratory level: intermediate Country: Tanzania World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 4%

Beyanga 2018 *(Continued)*

Index tests	Index: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: LJ Speciation: yes
Flow and timing	
Comparative	
Notes	10 samples had invalid Xpert MTB/RIF results, 16 results contaminated culture.

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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		

Beyanga 2018 *(Continued)*

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?	No	
Could the patient flow have introduced bias?		Low risk

Bjerrum 2016

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected adults screened for pulmonary TB irrespective of symptoms Age: 18 years and older, median 38 years (IQR 31 to 45) Sex, female: 64% HIV infection: 100% History of TB: 6% Sample size: 195 Clinical setting: both outpatient and inpatient Laboratory level: central Country: Ghana World Bank Income Classification: middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 17.9%
Index tests	Index: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: LJ and MGIT 960

Bjerrum 2016 *(Continued)*

	Speciation: yes		
Flow and timing			
Comparative			
Notes	Screening study		

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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			

Bjerrum 2016 *(Continued)*

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

Dorman 2012

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: miners attending occupational health services for annual examination, irrespective of signs and symptoms Age: 43 years (34-49) Sex, female: 6.1% HIV infection: 14% positive, 50% unknown History of TB: 12% Sample size: 6893 Clinical setting: outpatient (mine) Laboratory level: intermediate Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: MGIT 960 Speciation: yes
Flow and timing	272/6893 (3.9%) specimens had invalid Xpert MTB/RIF or contaminated culture; although not included, these participants were accounted for
Comparative	
Notes	

Dorman 2012 *(Continued)*

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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	

Heidebrecht 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: irrespective of symptoms. 45% had signs and symptoms of TB. Age: adults median 41 years (IQR 31-57) Sex, female: 65% HIV infection: 62% History of TB: 23% Sample size: 215 Clinical setting: inpatient medical ward Laboratory level: intermediate Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 23%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 and Middlebrook Speciation: yes
Flow and timing	Of 215 patients with Xpert, only 125 also had culture performed (on 2nd sample). 2nd sample for reference testing unobtainable for nearly 40% of participants. Total data come from 125 pairs.
Comparative	
Notes	6/27 Xpert MTB/RIF negative patients were diagnosed with extrapulmonary TB

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Heidebrecht 2016 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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?	No		
Could the patient flow have introduced bias?		High risk	

Henostroza 2016

Study characteristics

Henostroza 2016 *(Continued)*

Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: ART-naïve people presenting for initiation of HIV care Age: 16 years and older, median 34 years (IQR 29 to 40) Sex, female: 49% HIV infection: 100% History of TB: not reported Sample size: 332 Clinical setting: outpatient Laboratory level: central Country: Zambia World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 18.6%
Index tests	Index: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: LJ and MGIT 960 Speciation: yes
Flow and timing	
Comparative	
Notes	The paper states that outpatients in this cohort were likely to have been less ill than hospitalized patients

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Henostroza 2016 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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	

Kempker 2019

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: newly diagnosed HIV+ patients, irrespective of symptoms. 63% had >=1 WHO symptom Age: adults >=18 years, mean 42 (SD 10) Sex, female: 30%

Kempker 2019 *(Continued)*

	HIV infection: 100%, median CD4 count: 122 cells/mm3
	History of TB: 3%
	Sample size: 103 (131 enrolled, 103 provided sputum)
	Clinical setting: outpatient
	Laboratory level: intermediate
	Country: Georgia
	World Bank Income Classification: upper-middle income
	High TB burden country: no
	High MDR-TB burden country: no
	High TB/HIV burden country: no
	Prevalence of TB cases in the study: 12%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB
	Reference standard for pulmonary TB: LJ solid culture
	Speciation: yes
Flow and timing	
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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		

Kempker 2019 *(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 2: Index Test (Xpert Ultra)			
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	

LaCourse 2016

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: none reported. HIV-infected women accessing prevention of mother-to-child transmission services as part of antenatal care were eligible Age: 16 years and older, median 25 years (IQR 22 to 30) Sex, female: 100% HIV infection: 100% History of TB: 9% Sample size: 288 Clinical setting: outpatient Laboratory level: central

LaCourse 2016 *(Continued)*

	Country: Kenya World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 2.4%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 Speciation: yes
Flow and timing	
Comparative	
Notes	

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?	Unclear		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			

LaCourse 2016 *(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	

Lawn 2011

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected people with advanced immunodeficiency, irrespective of symptoms (most had 1 or more of the following TB symptoms: current cough, fever, night sweats, or weight loss) Age: median 34 years (IQR 28 to 41) Sex, female: 65.4% HIV infection: 100% History of TB: 26.5% Sample size: 394 Clinical setting: HIV anti-retroviral clinic; all participants were screened for TB Laboratory level: central Country: South Africa, Cape Town World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes

Lawn 2011 *(Continued)*

	High TB/HIV burden country: yes TB incidence rate: 993 per 100,000 MDR-TB prevalence: % MDR-TB among new TB cases = 0.9% (Source: survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: survey in Western Cape Province, 2002) Prevalence of TB cases in the study: 18.3%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: rifampicin resistance Reference standard for rifampicin resistance: culture-based DST (MGIT 960)
Flow and timing	
Comparative	
Notes	Lawn 2011 determined Xpert MTB/RIF accuracy for detection of rifampicin resistance, with respect to culture-based drug susceptibility testing. Xpert MTB/RIF accuracy for detection of TB, with respect to culture, is reported in Lawn 2012.

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			

Lawn 2011 *(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	

Lawn 2012

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected people with advanced immunodeficiency, irrespective of symptoms (most had 1 or more of the following TB symptoms: current cough, fever, night sweats, or weight loss) Age: median 34 years (IQR 28 to 41) Sex, female: 65.4% HIV infection: 100% History of TB: 26.5% Sample size: 394 Clinical setting: HIV anti-retroviral clinic; all participants were screened for TB Laboratory level: central Country: South Africa, Cape Town World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes

Lawn 2012 *(Continued)*

	TB incidence rate: 993 per 100,000 MDR-TB prevalence: % MDR-TB among new TB cases = 0.9% (Source: survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: survey in Western Cape Province, 2002) Prevalence of TB cases in the study: 18.3%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: MGIT 960 Speciation: yes Target condition: rifampicin resistance Reference standard for rifampicin resistance: MGIT 960
Flow and timing	
Comparative	
Notes	This study evaluated the use of Xpert MTB/RIF to screen HIV-infected people with advanced immunodeficiency enrolling in antiretroviral therapy services regardless of symptoms, although most participants in the study had TB symptoms. Of 3 participants with apparent false-positive Xpert MTB/RIF results, on follow-up 2 had overt pulmonary and systemic symptoms suggestive of TB and improved on anti-TB treatment. The 3rd participant was lost to follow-up. Median CD4 cell count, 171 cells/ml; IQR 102 to 236

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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		

Lawn 2012 *(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 2: Index Test (Xpert Ultra)			
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	

Lopez-Varela 2019

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected people at the time of HIV diagnosis, irrespective of symptoms (41.3% had 1 or more TB symptoms: current cough, fever, night sweats, or weight loss) Age: mean 35 years (SD 14) Sex, female: 56.4% HIV infection: 100% (median CD4 328, IQR 195 to 505) History of TB: 1.6% Sample size: 91 Clinical setting: home-based HIV counselling and testing

Lopez-Varela 2019 *(Continued)*

	Laboratory level: intermediate Country: Mozambique World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes TB incidence rate: 847 per 100,000 Prevalence of TB cases in the study: 4.4%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: liquid culture Speciation: yes
Flow and timing	
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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

Lopez-Varela 2019 *(Continued)*

DOMAIN 2: Index Test (Xpert Ultra)			
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	

Mollel 2017

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: 16 years and older, mean 42 years Sex, female: 55% HIV infection: 100% History of TB: not reported Sample size: 69 Clinical setting: outpatient Laboratory level: intermediate Country: Tanzania World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes

Mollel 2017 *(Continued)*

	Prevalence of TB cases in the study: 13.0%		
Index tests	Index test: Xpert MTB/RIF		
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: LJ Speciation: not reported		
Flow and timing			
Comparative			
Notes			

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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?	Unclear		

Mollel 2017 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
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

Ntinginya 2012

Study characteristics	
Patient Sampling	Cross-sectional study, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: household contacts enrolled irrespective of symptoms (15.5% reported >=1 TB symptom) Age: age >=5, mean 26 years (SD 17.6) Sex, female: 59.4% HIV infection: not assessed History of TB: 3% Sample size: 33 Clinical setting: community-based household contacts of TB patients Laboratory level: intermediate Country: Tanzania World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 15% of people who produced sputum; 2.3% of contacts overall
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: solid LJ or liquid MGIT 960

Ntinginya 2012 *(Continued)*

	Speciation: yes
Flow and timing	219 contacts approached; only 33 (15.1%) able to produce sputum and included in results
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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			

Ntinginya 2012 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	High risk

O'Grady 2012

Study characteristics	
Patient Sampling	Cross-sectional sampling, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: adult medical inpatients at tertiary hospital, regardless of symptoms or admission diagnosis (on TB treatment excluded from analysis) Age: adults >15 years, median age 35 years (IQR 28 to 43) HIV infection: 71% History of TB: unknown Sample size: 643 Clinical setting: tertiary hospital admitted patients Laboratory level: intermediate Country: Zambia World Bank Income Classification: low income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 31% of 643 patients not on treatment
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: MGIT 960 Speciatiation: yes
Flow and timing	881 admitted patients contributed to demographics above, of whom 643 not already on TB treatment and included in the analysis of sensitivity and specificity of Xpert MTB/RIF
Comparative	
Notes	

O'Grady 2012 *(Continued)*

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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	

Reeve 2019a

Study characteristics			
Patient Sampling	Cross-sectional study, consecutive enrolment, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: HIV+ adults initiating ART, irrespective of signs and symptoms. (52% reported at least 1 symptom) Sex, female: 62% HIV infection: 100% History of TB: not reported Sample size: 571 Clinical setting: outpatient ART clinic Laboratory level: intermediate Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 12%		
Index tests	Index test: Xpert MTB/RIF		
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: MGIT 960		
Flow and timing			
Comparative			
Notes			
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?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Reeve 2019a *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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	

Reeve 2019b

Study characteristics	
Patient Sampling	Cross-sectional study, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV+ adults initiating ART, irrespective of signs and symptoms. (52% reported at least 1 symptom) Sex, female: 62%

Reeve 2019b *(Continued)*

	HIV infection: 100% History of TB: not reported Sample size: 571 Clinical setting: outpatient ART clinic Laboratory level: intermediate Country: South Africa World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 12%
Index tests	Index test: Xpert Ultra
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: MGIT 960
Flow and timing	
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
DOMAIN 2: Index Test (Xpert Ultra)			
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		

Reeve 2019b *(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	

Santos 2020

Study characteristics	
Patient Sampling	Cross-sectional study, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: Adults residing in prisons, irrespective of signs and symptoms. (40% of total pop reported at least 1 sx, 80.4% of sputum providers reported at least 1 symptom) Sex, female: 0% HIV infection: not reported (2% in TB+) History of TB: 8% of screened population Sample size: N = 5387; N = 1385 with both Xpert & culture performed (remainder couldn't make sputum) Clinical setting: prisons Laboratory level: intermediate Country: Brazil

Santos 2020 *(Continued)*

	World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 7% (of persons tested/producing sputum)
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: TB culture (both MGIT & LJ available at reference lab)
Flow and timing	
Comparative	
Notes	3919 unable to produce sputum. 1467 (27%) provided sputum, 1385 participants had both Xpert & culture performed. Invalid/not done tests not included in analysis. Does not specify whether Mtb species identification performed on TB culture.

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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?			
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 2: Index Test (Xpert Ultra)			

Santos 2020 *(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?	No		
Could the patient flow have introduced bias?		High risk	

Tahseen 2018

Study characteristics	
Patient Sampling	Cross-sectional study, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: irrespective of symptoms Age: 18 years and older, median 30 (26-46) Sex, female: 0% HIV infection: 100% History of TB: 9% Sample size: 635 Clinical setting: outpatient IVDU treatment centre Laboratory level: intermediate Country: Pakistan World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: no

Tahseen 2018 *(Continued)*

	Prevalence of TB cases in the study: 13.0%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard: LJ and MGIT 960 Speciaiton: yes
Flow and timing	12 invalid Xpert; 30 contaminated cultures in 635 participants, not included in analysis
Comparative	
Notes	

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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		

Tahseen 2018 *(Continued)*

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	

Yoon 2017

Study characteristics	
Patient Sampling	Cross-sectional design, consecutive enrolment, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: HIV-positive people initiating antiretroviral therapy Age: 18 years and older, median 33 years (IQR 27 to 40) Sex, female: 53% HIV infection: 100% History of TB: 4% Sample size: 1177 Clinical setting: outpatient HIV/AIDS clinics Laboratory level: central Country: Uganda World Bank Income Classification: middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: yes Prevalence of TB cases in the study: 13.8%
Index tests	Index test: Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary TB Reference standard for pulmonary TB: LJ and MGIT 960

Yoon 2017 *(Continued)*

	Speciation: yes		
Flow and timing			
Comparative			
Notes			

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?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
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 2: Index Test (Xpert Ultra)			
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			

Yoon 2017 *(Continued)*

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

ART: antiretroviral therapy; **IQR:** interquartile range; **MDR:** multidrug-resistant; **MGIT:** Mycobacteria Growth Indicator Tube; **SD:** standard deviation; **TB:** tuberculosis.

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

Study	Reason for exclusion
Adams 2015	persons not screened irrespective of symptoms
Adejumo 2018	persons not screened irrespective of symptoms
Adetunji 2019	no microbiological reference standard (TB culture)
Agizew 2017	persons not screened irrespective of symptoms
Aia 2016	persons not screened irrespective of symptoms
Antonenka 2013	persons not screened irrespective of symptoms
Ardizzoni 2015	persons not screened irrespective of symptoms
Ardizzoni 2020	persons not screened irrespective of symptoms
Assefa 2019	no microbiological reference standard (TB culture)
Auld 2016a	not original research
Auld 2016b	persons not screened irrespective of symptoms
Auld 2020	no microbiological reference standard (TB culture)
Awan 2018	persons not screened irrespective of symptoms
Ayala 2016	persons not screened irrespective of symptoms
Bablishvili 2015	persons not screened irrespective of symptoms
Bacells 2016	Xpert used on a non-respiratory sample
Balcha 2014a	duplicate data from another study
Balcha 2015	duplicate data from another study
Basir 2019	no microbiological reference standard (TB culture)

Study	Reason for exclusion
Bassett 2019	no microbiological reference standard (TB culture)
Benjamin 2019	persons not screened irrespective of symptoms
Bhardwaj 2019	persons not screened irrespective of symptoms
Bjerrum 2015	number of positive tests not reported
Blakemore 2011	persons not screened irrespective of symptoms
Boum 2016	persons not screened irrespective of symptoms
Byashalira 2019	persons not screened irrespective of symptoms
Calligaro 2017	data not disaggregated on persons screened with or regardless of symptoms
Carmone 2017	no microbiological reference standard (TB culture)
Cavanaugh 2016	data insufficient for 2x2 table
Celik 2015	persons not screened irrespective of symptoms
Charoensook 2018	persons not screened irrespective of symptoms
Chry 2020	persons not screened irrespective of symptoms
Chumpa 2020	persons not screened irrespective of symptoms
Deshmukh 2020	persons not screened irrespective of symptoms
Ekeke 2020	persons not screened irrespective of symptoms
Farra 2017	persons not screened irrespective of symptoms
Floridia 2017	no microbiological reference standard (TB culture)
Gautam 2019	persons not screened irrespective of symptoms
Gelalcha 2017	persons not screened irrespective of symptoms
Gizachew 2017	persons not screened irrespective of symptoms
Gupta-Wright 2018	no microbiological reference standard (TB culture)
Gursoy 2016	persons not screened irrespective of symptoms
Habeenzu 2017	persons not screened irrespective of symptoms
Habte 2016	persons not screened irrespective of symptoms
Hanifa 2016	no microbiological reference standard (TB culture)
Head 2019	persons not screened irrespective of symptoms
Hiruy 2018	persons not screened irrespective of symptoms

Study	Reason for exclusion
Ho 2016	no microbiological reference standard (TB culture)
Hosseinipour 2016	no microbiological reference standard (TB culture)
Huang 2018	persons not screened irrespective of symptoms
Huerga 2020	persons not screened irrespective of symptoms
Huh 2019	Xpert used on a non-respiratory sample
Kamenska 2019	persons not screened irrespective of symptoms
Kerkhoff 2014	Xpert used on a non-respiratory sample
Kurbaniyazova 2017	data not disaggregated on persons screened with or regardless of symptoms
Kuyinu 2018	persons not screened irrespective of symptoms
LaCourse 2014	paediatric population
LaCourse 2018	paediatric population
Lawn 2012a	duplicate data from another study
Lawn 2012b	duplicate data from another study
Lawn 2013	duplicate data from another study
Lawn 2015	data insufficient for 2x2 table
Lawn 2017	duplicate data from another study
Lebina 2016	no microbiological reference standard (TB culture)
Lima 2020	persons not screened irrespective of symptoms
Luo 2019	persons not screened irrespective of symptoms
Maria 2018	persons not screened irrespective of symptoms
Marks 2019	no microbiological reference standard (TB culture)
Marlowe 2011	persons not screened irrespective of symptoms
Mbatchou 2019	data insufficient for 2x2 table
Mbu 2018	data insufficient for 2x2 table
Meng 2017	persons not screened irrespective of symptoms
Metcalfe 2015	persons not screened irrespective of symptoms
Metcalfe 2016	persons not screened irrespective of symptoms
Miller 2011	persons not screened irrespective of symptoms

Study	Reason for exclusion
Mishra 2020	persons not screened irrespective of symptoms
Modi 2016	data insufficient for 2x2 table
Morishita 2017	persons not screened irrespective of symptoms
Nathavitharana 2017	persons not screened irrespective of symptoms
Nicol 2018	persons not screened irrespective of symptoms
Nikolayevskyy 2019	persons not screened irrespective of symptoms
Ou 2019	persons not screened irrespective of symptoms
Ozkutuk 2014	persons not screened irrespective of symptoms
Parcell 2017	persons not screened irrespective of symptoms
Park 2013	persons not screened irrespective of symptoms
Pimkina 2015	persons not screened irrespective of symptoms
Ramamurthy 2016	persons not screened irrespective of symptoms
Reepalu 2016	data insufficient for 2x2 table
Reis 2019	persons not screened irrespective of symptoms
Sarinoglu 2020	persons not screened irrespective of symptoms
Semitala 2019	no microbiological reference standard (TB culture)
Shah 2019	paediatric population
Sun 2019	persons not screened irrespective of symptom
Teo 2011	persons not screened irrespective of symptom
Trajman 2014	persons not screened irrespective of symptom
van Kampen 2015	persons not screened irrespective of symptom
Van Rie 2011	not original research
Yasemin 2019	persons not screened irrespective of symptom
Yoon 2019	duplicate data from another study

DATA

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

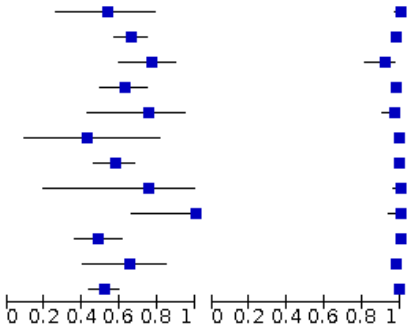
Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Xpert MTB/RIF, HIV positive, irrespective of TB symptoms	12	4775
2 Xpert Ultra, HIV, irrespective of TB symptoms	1	571
3 Xpert MTB/RIF, household contacts, irrespective of TB symptoms	2	508
4 Xpert MTB/RIF, prisoners, irrespective of TB symptoms	2	1827
5 Xpert MTB/RIF, miners, irrespective of TB symptoms	1	6621
6 Xpert MTB/RIF, admitted patients, irrespective of TB symptoms	2	768
7 Xpert MTB/RIF, all high-risk groups	18	13114
8 Xpert MTB/RIF for rifampicin resistance	3	159

Test 1. Xpert MTB/RIF, HIV positive, irrespective of TB symptoms

Xpert MTB/RIF, HIV positive, irrespective of TB symptoms

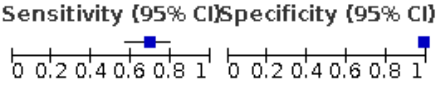
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Darraji 2013	8	0	7	110	0.53 [0.27, 0.79]	1.00 [0.97, 1.00]
Balcha 2014	81	13	41	677	0.66 [0.57, 0.75]	0.98 [0.97, 0.99]
Bjerrum 2016	27	5	8	55	0.77 [0.60, 0.90]	0.92 [0.82, 0.97]
Henostroza 2016	39	5	23	256	0.63 [0.50, 0.75]	0.98 [0.96, 0.99]
Kempker 2019	9	3	3	88	0.75 [0.43, 0.95]	0.97 [0.91, 0.99]
LaCourse 2016	3	1	4	280	0.43 [0.10, 0.82]	1.00 [0.98, 1.00]
Lawn 2012	49	4	36	427	0.58 [0.46, 0.68]	0.99 [0.98, 1.00]
Lopez-Varela 2019	3	0	1	87	0.75 [0.19, 0.99]	1.00 [0.96, 1.00]
Mollel 2017	9	0	0	60	1.00 [0.66, 1.00]	1.00 [0.94, 1.00]
Reeve 2019a	33	1	35	502	0.49 [0.36, 0.61]	1.00 [0.99, 1.00]
Tahseen 2018	13	11	7	574	0.65 [0.41, 0.85]	0.98 [0.97, 0.99]
Yoon 2017	84	8	79	1006	0.52 [0.44, 0.59]	0.99 [0.98, 1.00]



Test 2. Xpert Ultra, HIV, irrespective of TB symptoms

Xpert Ultra, HIV, irrespective of TB symptoms

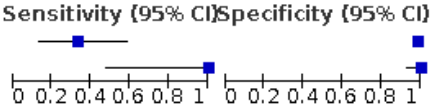
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Reeve 2019b	47	9	21	494	0.69 [0.57, 0.80]	0.98 [0.97, 0.99]



Test 3. Xpert MTB/RIF, household contacts, irrespective of TB symptoms

Xpert MTB/RIF, household contacts, irrespective of TB symptoms

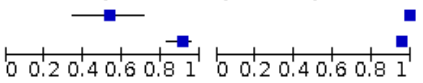
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beyanga 2018	6	7	12	427	0.33 [0.13, 0.59]	0.98 [0.97, 0.99]
Ntinginya 2012	5	0	0	51	1.00 [0.48, 1.00]	1.00 [0.93, 1.00]



Test 4. Xpert MTB/RIF, prisoners, irrespective of TB symptoms

Xpert MTB/RIF, prisoners, irrespective of TB symptoms

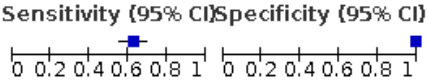
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Al-Darraji 2016	16	4	14	408	0.53 [0.34, 0.72]	0.99 [0.98, 1.00]		
Santos 2020	88	65	9	1223	0.91 [0.83, 0.96]	0.95 [0.94, 0.96]		



Test 5. Xpert MTB/RIF, miners, irrespective of TB symptoms

Xpert MTB/RIF, miners, irrespective of TB symptoms

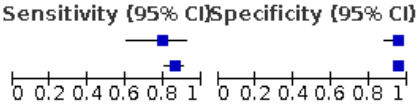
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2012	117	27	70	6407	0.63 [0.55, 0.70]	1.00 [0.99, 1.00]		



Test 6. Xpert MTB/RIF, admitted patients, irrespective of TB symptoms

Xpert MTB/RIF, admitted patients, irrespective of TB symptoms

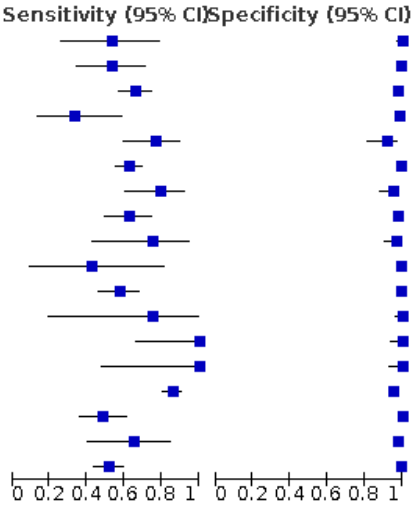
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Heidebrecht 2016	23	5	6	91	0.79 [0.60, 0.92]	0.95 [0.88, 0.98]		
O'Grady 2012	173	22	28	420	0.86 [0.80, 0.91]	0.95 [0.93, 0.97]		



Test 7. Xpert MTB/RIF, all high-risk groups

Xpert MTB/RIF, all high-risk groups

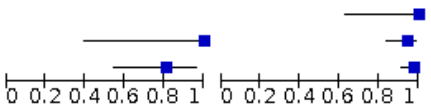
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Al-Darraji 2013	8	0	7	110	0.53 [0.27, 0.79]	1.00 [0.97, 1.00]		
Al-Darraji 2016	16	4	14	408	0.53 [0.34, 0.72]	0.99 [0.98, 1.00]		
Balcha 2014	81	13	41	677	0.66 [0.57, 0.75]	0.98 [0.97, 0.99]		
Beyanga 2018	6	7	12	427	0.33 [0.13, 0.59]	0.98 [0.97, 0.99]		
Bjerrum 2016	27	5	8	55	0.77 [0.60, 0.90]	0.92 [0.82, 0.97]		
Dorman 2012	117	27	70	6407	0.63 [0.55, 0.70]	1.00 [0.99, 1.00]		
Heidebrecht 2016	23	5	6	91	0.79 [0.60, 0.92]	0.95 [0.88, 0.98]		
Henostroza 2016	39	5	23	256	0.63 [0.50, 0.75]	0.98 [0.96, 0.99]		
Kempker 2019	9	3	3	88	0.75 [0.43, 0.95]	0.97 [0.91, 0.99]		
LaCourse 2016	3	1	4	280	0.43 [0.10, 0.82]	1.00 [0.98, 1.00]		
Lawn 2012	49	4	36	427	0.58 [0.46, 0.68]	0.99 [0.98, 1.00]		
Lopez-Varela 2019	3	0	1	87	0.75 [0.19, 0.99]	1.00 [0.96, 1.00]		
Mollel 2017	9	0	0	60	1.00 [0.66, 1.00]	1.00 [0.94, 1.00]		
Ntinginya 2012	5	0	0	51	1.00 [0.48, 1.00]	1.00 [0.93, 1.00]		
O'Grady 2012	173	22	28	420	0.86 [0.80, 0.91]	0.95 [0.93, 0.97]		
Reeve 2019a	33	1	35	502	0.49 [0.36, 0.61]	1.00 [0.99, 1.00]		
Tahseen 2018	13	11	7	574	0.65 [0.41, 0.85]	0.98 [0.97, 0.99]		
Yoon 2017	84	8	79	1006	0.52 [0.44, 0.59]	0.99 [0.98, 1.00]		



Test 8. Xpert MTB/RIF for rifampicin resistance

Xpert MTB/RIF for rifampicin resistance

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Darraji 2013	0	0	0	8	Not estimable	1.00 [0.63, 1.00]
Lawn 2011	4	3	0	48	1.00 [0.40, 1.00]	0.94 [0.84, 0.99]
O'Grady 2012	13	2	3	78	0.81 [0.54, 0.96]	0.97 [0.91, 1.00]



ADDITIONAL TABLES

Table 1. Xpert MTB/RIF as a screening test for pulmonary tuberculosis in people irrespective of tuberculosis signs and symptoms, against culture

Analysis group	Number of studies (participants)	Number (%) with pulmonary TB	Median pooled sensitivity (95% CrI)	Median pooled specificity (95% CrI)	Positive predictive value (95% CrI) (0.5%)	Negative predictive value (95% CrI) (0.5%)	Positive predictive value (95% CrI) (5%)	Negative predictive value (95% CrI) (5%)
HIV positive	12 (4775)	602 (12.6)	61.8% (53.6 to 69.9)	98.8% (98.0 to 99.4)	20.7% (14.3 to 31.6)	99.8% (99.8 to 99.9)	73.7% (63.6 to 83.4)	98.8% (98.0 to 99.4)
HIV positive ≥ 50% symptoms	9 (3791)	571 (15.1)	62.9% (53.9 to 72.1)	98.7% (97.7 to 99.4)	19.7% (12.2 to 32.2)	99.8% (99.8 to 99.9)	72.0% (59.7 to 83.4)	98.1% (97.6 to 98.5)
HIV positive < 50% symptoms	3 (984)	31 (3.2)	61.1% (35.5 to 82.3)	99.1% (97.6 to 99.8)	25.3% (10.2 to 60.0)	99.8% (99.7 to 99.9)	77.8% (54.5 to 93.6)	98.0% (96.7 to 99.1)
High-risk groups[a], combined	5 (8956)	337 (3.8)	69.4% (47.7 to 86.2)	98.8% (97.2 to 99.5)	86.1% (72.6 to 94.0)	96.7% (94.5 to 98.5)	73.2% (64.8 to 81.2)	98.2% (97.8 to 98.5)

[a]High-risk groups include household contacts, people residing in prisons, and miners.
Predictive values were calculated at 0.5% and 5% pre-test probability.

APPENDICES

Appendix 1. Search strategy

MEDLINE (PubMed)

Search	Query
#1	Search Tuberculosis or MDR-TB or XDR-TB or tuberculous Field: Title/Abstract
#2	Search “Mycobacterium tuberculosis” [Mesh]
#3	Search "Tuberculosis"[Mesh] or ("Tuberculosis, Multidrug-Resistant"[Mesh]) OR "Extensively Drug-Resistant Tuberculosis"[Mesh]
#4	Search ((#3) OR #2) OR #1
#5	Search Xpert* or GeneXpert or Ultra or cepheid Field: Title/Abstract
#6	Search "near* patient*" or near-patient Field: Title/Abstract
#7	Search (#6) OR #5
#8	Search "active case" Field: Title/Abstract
#9	Search "case finding" Field: Title/Abstract
#10	Search prevalence Field: Title/Abstract
#11	Search Asymptomatic Field: Title/Abstract
#12	Search comorbidity or co-morbidity Field: Title/Abstract
#13	Search screening Field: Title/Abstract
#14	Search Detect* or missed or undetect* or undiagnosed Field: Title/Abstract
#15	Search ((((((#14) OR #13) OR #12) OR #11) OR #10) OR #9) OR #8
#16	Search (#4) AND #7 AND #15

Database: Embase 1947-present, updated daily

Search Strategy:

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1 (tuberculosis or TB).mp.
2 Tuberculosis, Multidrug-Resistant/ or Extensively Drug-Resistant Tuberculosis/ or Tuberculosis/ or tuberculosis.mp. or Mycobacterium tuberculosis/
3 (MDR-TB or XDR-TB).mp.
4 1 or 2 or 3
5 Xpert* MTB RIF.ti. or Xpert* MTB RIF.ab.
6 (Xpert* or GeneXpert or cepheid).mp.
7 (near* patient or near-patient).ti. or (near* patient or near-patient).ab.
8 5 or 6 or 7
9 4 and 8
10 detection.mp.

11 diagnostic error/ or missed.mp.
12 (undetected or undiagnosed).mp.
13 asymptomatic.mp.
14 comorbidity.mp. or comorbidity/
15 prevalence/
16 active case finding.mp. or case finding/
17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 9 and 17

Web of Science

#	3	#2 AND #1 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#	2	**TOPIC:** (asymptomatic or undetected or undiagnosed) *OR* **TOPIC:** ("case finding" or prevalence or comorbidity) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years
#	1	**TOPIC:** (tuberculosis OR tb OR mycobacterium) *AND* **TOPIC:** (xpert* OR genexpert OR cepheid) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years

Scopus

(TITLE-ABS-KEY (tuberculosis OR tb OR mycobacterium) AND TITLE-ABS-KEY ((xpert* OR genexpert OR cepheid)) AND TITLE-ABS-KEY (asymptomatic OR undetected OR undiagnosed OR "case finding" OR prevalence OR comorbidity))

LILACS

(tuberculosis OR TB OR mycobacterium) (Words) AND (xpert$ OR Genexpert OR Cepheid) (Words)

Cochrane Infectious Diseases Specialized Register

(tuberculosis or TB) and (xpert* or Genexpert or Cepheid)

Clinicaltrials.gov, WHO ICTRP, ISRCTN:

Tuberculosis and Genexpert

Tuberculosis and Xpert

ProQuest Dissertations & Theses

tuberculosis and (Xpert or genexpert)

Appendix 2. QUADAS-2

In QUADAS-2, we assessed methodological quality separately for each of the objectives, Xpert for pulmonary tuberculosis detection and Xpert for rifampicin resistance detection.

Domain 1: patient selection

Xpert MTB/RIF and Xpert Ultra for 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 patients; 'no' if the study selected patients by convenience; and 'unclear' if the study did not report the manner of patient selection or we could not tell.

Signalling question 2: did the study avoid inappropriate exclusions? We answered 'yes' if the study included all individuals in the general population or the high-risk group considered for tuberculosis screening. We answered 'no' if the study primarily or exclusively included individuals with a history of tuberculosis; individuals who had undergone previous treatment (retreatment patients); or those with signs and symptoms of tuberculosis. We answered 'unclear' if we could not tell.

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

We were interested in how Xpert MTB/RIF or Xpert Ultra performed in patients who were evaluated as they would be in the settings of intended use. We answered 'low concern' if the study population resembled a population that was selected for tuberculosis screening in community settings or primary care centres. We answered 'high concern' if the study population does not resemble a population that was selected for tuberculosis screening in a community setting. We answered 'unclear concern' if there was insufficient information to make a decision.

Xpert MTB/RIF and Xpert Ultra for detection of rifampicin resistance

Domain 1: patient selection is the same as for MTB/RIF or Xpert Ultra for detection of pulmonary tuberculosis.

Domain 2: index test

Xpert MTB/RIF and Xpert Ultra for 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 this question 'yes' for all studies because Xpert test results were automatically generated and the user was provided with printable test results. Thus, there is no room for subjective interpretation of test results.

Signalling *question 2: if a threshold was used, was it prespecified?* The threshold was prespecified in all versions of Xpert. We answered this question 'yes' for all studies.

For risk of bias, we judge 'low concern' 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. All steps in the Xpert MTB/RIF and Xpert Ultra assays are completely automated and self-contained following sample loading. We answered 'low concern' if the index test was performed as recommended by the manufacturer, which we had anticipated would be true for most studies. We answered 'unclear concern' if the ratio of the Xpert MTB/RIF or Xpert Ultra sample reagent: specimen volume was not 2:1 for a raw specimen or 3:1 for a sediment, as recommended by the manufacturer.

Xpert MTB/RIF and Xpert Ultra for detection of rifampicin resistance

Domain 2: index test is the same as for MTB/RIF or Xpert Ultra for detection of pulmonary tuberculosis.

Domain 3: reference standard

Xpert MTB/RIF and Xpert Ultra for 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, since culture as a reference standard was 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 (for example, MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We answered 'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert MTB/RIF or Xpert Ultra test result. We answered 'unclear' if we could not tell.

Applicability: are there concerns that the target condition as defined by the reference standard does not match the question? We answered 'high concern' if included studies did not speciate mycobacteria isolated in culture; 'low concern' if speciation was performed; and 'unclear concern' if we could not tell.

Xpert MTB/RIF and Xpert Ultra for detection of rifampicin resistance

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

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

We answered 'yes' if either culture-based drug susceptibility testing (DST) or line probe assay (such as MTBDR*plus)* was used. These are the criteria for inclusion for this objective of 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 (for example, MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We answered 'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert MTB/RIF or Xpert Ultra test result. We will answer 'unclear' if we could not tell.

Applicability: are there concerns that the target condition as defined by the reference standard does not match the question? We judged applicability to be of 'low concern' for those studies evaluating Xpert MTB/RIF or Xpert Ultra for rifampicin resistance because these specimens had already been identified as *Mycobacterium tuberculosis* positive.

Domain 4: flow and timing

Xpert MTB/RIF and Xpert Ultra for detection of pulmonary tuberculosis detection

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 included studies, we expected that specimens for Xpert MTB/RIF or Xpert Ultra and culture would be obtained at the same time, when patients were screened. However, even if there were a delay of several days between index test and reference standard, tuberculosis is a chronic disease and we considered misclassification of disease status to be unlikely, as long as treatment was not initiated in the interim. We answered 'yes' if the index test and reference standard were performed at the same time or if the time interval was less than or equal to seven days, 'no' if the time interval was greater than seven days, and 'unclear' if we could not tell.

Signalling *question 2: did all patients receive the same reference standard?* We answered this question 'yes' for all studies as an acceptable reference standard (either solid or liquid culture) was specified as a criterion for inclusion in the review. However, we acknowledge that it is possible that some specimens could undergo solid culture and others liquid culture. This could potentially result in variations in accuracy, but we thought the variation would be minimal.

Signalling *question 3: were all patients included in the analysis?* We determined the answer to this question by comparing the number of patients enrolled with the number of patients included in the 2 x 2 tables. We answered 'yes' if the numbers matched and 'no' if there were patients enrolled in the study that were not included in the analysis. We answered 'unclear' if we could not tell.

Xpert MTB/RIF and Xpert Ultra for detection of rifampicin resistance

Domain 4: flow and timing is the same as for Xpert MTB/RIF or Xpert Ultra 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.

HISTORY

Protocol first published: Issue 7, 2020
Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

AES, JMR, MK, KRS, and DJH drafted the manuscript. ND and IS wrote the statistical analysis section. All review authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

AES received funding from USAID, administered by the World Health Organization Global TB Programme, Switzerland. She has received salary compensation from the University of Washington, where she is an Acting Assistant Professor in Global Health and Medicine/Infectious Diseases. A portion of her salary derives from NIH grants and from grants from the Bill & Melinda Gates Foundation.

JMR received funding from USAID, administered by the World Health Organization Global TB Programme, Switzerland. JMR has grants/grants pending to her host institution from US National Institutes of Health, KNCV TB Foundation, and The Global Fund to Fight AIDS, TB, and Malaria, The Firland Foundation.

MY has no known conflicts of interest to declare.

IS has no known conflicts of interest to declare.

MK has received funding from USAID, administered by the World Health Organization Global TB Programme, Switzerland for related systematic reviews.

ND has no known conflicts of interest to declare.

KRS has received financial support from Cochrane Infectious Diseases, UK, McGill University, Canada, and USAID, USA, administered by the World Health Organization (WHO) Global TB Programme, Switzerland, for the preparation of systematic reviews and educational materials, consultancy fees from Foundation for Innovative New Diagnostics (FIND), Switzerland (for the preparation of systematic reviews and GRADE tables), honoraria, and travel support to attend WHO guideline meetings.

DJH has received funding from USAID, administered by the World Health Organization Global TB Programme, Switzerland for related systematic reviews.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Objectives: we intended to assess Xpert MTB/RIF and Xpert Ultra as screening tests for pulmonary tuberculosis in the general population, irrespective of signs and symptoms. However, we did not identify any studies conducted in the general population.

Types of studies: We included abstracts with sufficient data to populate 2x2 contingency tables.

Statistical analysis and data synthesis: we performed a post-hoc analysis by combining several high-risk groups into a single pooled analysis of sensitivity and specificity in adults at high risk for tuberculosis. These high-risk groups included household contacts of people with tuberculosis, people residing in prisons, and miners. We had planned to compare the accuracy of Xpert MTB/RIF and Xpert Ultra by first including all studies with relevant data, i.e. both indirect and direct comparisons, and then by restricting the analyses to studies that made comparisons between Xpert MTB/RIF and Xpert Ultra in the same participants, i.e. direct comparisons. However, there were insufficient data to perform these comparisons. We stated in the protocol that we would provide predictive sensitivity and specificity. We did not do this. However, instead, we estimated positive and negative predictive values at pre-specified pre-test probabilities recommended by the WHO (0.5% and 5%) as we considered these values more useful for clinicians.

Subgroup analyses: we intended to perform subgroup analyses among studies conducted in high versus not high tuberculosis burden countries, and similarly for high TB/HIV burden and high MDR-TB burden versus not high burden countries. However, most studies were conducted in high burden countries, therefore we did not perform these subgroup analyses.

Sensitivity analyses: we had planned to perform sensitivity analyses limiting the analyses to studies that accounted for all participants in the analysis, studies that used liquid culture as the reference standard, and studies where a consecutive or random sample of participants were enrolled. However, all studies met these criteria, therefore we were unable to perform these sensitivity analyses.

Uninterpretable results: regarding uninterpretable results, in the protocol we wrote we would use a Bayesian hierarchical model for a single proportion to estimate the pooled proportion of uninterpretable index test results. However, most studies in this review did not report uninterpretable results, so we did not model them separately.

Non-stigmatising language: whenever possible, we re-categorized high-risk groups using non-stigmatising language. For example, we changed the category "homeless people" to "people experiencing homelessness."