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Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis (Review)

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[Diagnostic Test Accuracy Review]

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

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ABSTRACT

Background

Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) are World Health Organization (WHO)-recommended rapid tests that simultaneously detect tuberculosis and rifampicin resistance in people with signs and symptoms of tuberculosis. This review builds on our recent extensive Cochrane Review of Xpert MTB/RIF accuracy.

Objectives

To compare the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis and detection of rifampicin resistance in adults with presumptive pulmonary tuberculosis. For pulmonary tuberculosis and rifampicin resistance, we also investigated potential sources of heterogeneity.

We also summarized the frequency of Xpert Ultra trace-positive results, and estimated the accuracy of Xpert Ultra after repeat testing in those with trace-positive results.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, Embase, Science Citation Index, Web of Science, LILACS, Scopus, the WHO ICTRP, the ISRCTN registry, and ProQuest to 28 January 2020 with no language restriction.

Selection criteria

We included diagnostic accuracy studies using respiratory specimens in adults with presumptive pulmonary tuberculosis that directly compared the index tests. For pulmonary tuberculosis detection, the reference standards were culture and a composite reference standard. For rifampicin resistance, 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, including data by smear and HIV status. We assessed risk of bias using QUADAS-2 and QUADAS-C. We performed meta-analyses comparing pooled sensitivities and specificities, separately for pulmonary tuberculosis detection and rifampicin resistance detection, and separately by reference standard. Most analyses used a bivariate random-effects model. For tuberculosis detection, we estimated accuracy in studies in participants who were not selected based on prior microscopy testing or history of tuberculosis. We performed subgroup analyses by smear status, HIV status, and history of tuberculosis. We summarized Xpert Ultra trace results.

Main results

We identified nine studies (3500 participants): seven had unselected participants (2834 participants). All compared Xpert Ultra and Xpert MTB/RIF for pulmonary tuberculosis detection; seven studies used a paired comparative accuracy design, and two studies used a randomized design. Five studies compared Xpert Ultra and Xpert MTB/RIF for rifampicin resistance detection; four studies used a paired design, and one study used a randomized design. Of the nine included studies, seven (78%) were mainly or exclusively in high tuberculosis burden countries. For pulmonary tuberculosis detection, most studies had low risk of bias in all domains.

Pulmonary tuberculosis detection

Xpert Ultra 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) (7 studies, 2834 participants; high-certainty evidence) versus Xpert MTB/RIF pooled sensitivity and specificity of 84.7% (78.6 to 89.9) and 98.4% (97.0 to 99.3) (7 studies, 2835 participants; high-certainty evidence). The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at 6.3% (0.1 to 12.8) for sensitivity and −2.7% (−5.7 to −0.5) for specificity. If the point estimates for Xpert Ultra and Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients, where 10% of those presenting with symptoms have pulmonary tuberculosis, Xpert Ultra will miss 9 cases, and Xpert MTB/RIF will miss 15 cases. The number of people wrongly diagnosed with pulmonary tuberculosis would be 40 with Xpert Ultra and 14 with Xpert MTB/RIF.

In smear-negative, culture-positive participants, pooled sensitivity was 77.5% (67.6 to 85.6) for Xpert Ultra versus 60.6% (48.4 to 71.7) for Xpert MTB/RIF; pooled specificity was 95.8% (92.9 to 97.7) for Xpert Ultra versus 98.8% (97.7 to 99.5) for Xpert MTB/RIF (6 studies).

In people living with HIV, pooled sensitivity was 87.6% (75.4 to 94.1) for Xpert Ultra versus 74.9% (58.7 to 86.2) for Xpert MTB/RIF; pooled specificity was 92.8% (82.3 to 97.0) for Xpert Ultra versus 99.7% (98.6 to 100.0) for Xpert MTB/RIF (3 studies).

In participants with a history of tuberculosis, pooled sensitivity was 84.2% (72.5 to 91.7) for Xpert Ultra versus 81.8% (68.7 to 90.0) for Xpert MTB/RIF; pooled specificity was 88.2% (70.5 to 96.6) for Xpert Ultra versus 97.4% (91.7 to 99.5) for Xpert MTB/RIF (4 studies).

The proportion of Ultra trace-positive results ranged from 3.0% to 30.4%. Data were insufficient to estimate the accuracy of Xpert Ultra repeat testing in individuals with initial trace-positive results.

Rifampicin resistance detection

Pooled sensitivity and specificity were 94.9% (88.9 to 97.9) and 99.1% (97.7 to 99.8) (5 studies, 921 participants; high-certainty evidence) for Xpert Ultra versus 95.3% (90.0 to 98.1) and 98.8% (97.2 to 99.6) (5 studies, 930 participants; high-certainty evidence) for Xpert MTB/RIF. The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at −0.3% (−6.9 to 5.7) for sensitivity and 0.3% (−1.2 to 2.0) for specificity. If the point estimates for Xpert Ultra and Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients, where 10% of those presenting with symptoms have rifampicin resistance, Xpert Ultra will miss 5 cases, and Xpert MTB/RIF will miss 5 cases. The number of people wrongly diagnosed with rifampicin resistance would be 8 with Xpert Ultra and 11 with Xpert MTB/RIF.

We identified a higher number of rifampicin resistance indeterminate results with Xpert Ultra, pooled proportion 7.6% (2.4 to 21.0) compared to Xpert MTB/RIF pooled proportion 0.8% (0.2 to 2.4). The estimated difference in the pooled proportion of indeterminate rifampicin resistance results for Xpert Ultra versus Xpert MTB/RIF was 6.7% (1.4 to 20.1).

Authors' conclusions

Xpert Ultra has higher sensitivity and lower specificity than Xpert MTB/RIF for pulmonary tuberculosis, especially in smear-negative participants and people living with HIV. Xpert Ultra specificity was lower than that of Xpert MTB/RIF in participants with a history of tuberculosis. The sensitivity and specificity trade-off would be expected to vary by setting. For detection of rifampicin resistance, Xpert Ultra and Xpert MTB/RIF had similar sensitivity and specificity. Ultra trace-positive results were common.

Xpert Ultra and Xpert MTB/RIF provide accurate results and can allow rapid initiation of treatment for rifampicin-resistant and multidrug-resistant tuberculosis.

PLAIN LANGUAGE SUMMARY

Xpert Ultra compared to Xpert MTB/RIF for diagnosing pulmonary tuberculosis and rifampicin resistance in adults

Why is improving the diagnosis of pulmonary tuberculosis important?

Tuberculosis is one of the leading causes of death worldwide. While tuberculosis is largely curable when detected early and effectively treated, around 1.2 million people died of tuberculosis in 2019. Xpert MTB/RIF and Xpert Ultra (the newest version) are World Health Organization-recommended rapid tests that simultaneously detect tuberculosis and rifampicin resistance in people with tuberculosis symptoms. Rifampicin is an important antituberculosis drug. Not recognizing tuberculosis when it is present (false negative) may result in severe illness and death, and an increased risk of infecting others. An incorrect diagnosis of tuberculosis (false positive) may result in anxiety, additional testing, unnecessary treatment, and medication side effects.

What is the aim of this review?

To determine how accurate Xpert Ultra is compared with Xpert MTB/RIF for diagnosing pulmonary tuberculosis and rifampicin resistance in adults. An extensive review of Xpert MTB/RIF accuracy was recently published as a Cochrane Review.

What was studied in this review?

We compared the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF with results primarily measured against culture (detection of pulmonary tuberculosis) and drug susceptibility testing and line probe assays (detection of rifampicin resistance).

What are the main results in this review?

Nine studies (3500 participants) compared Xpert Ultra to Xpert MTB/RIF for diagnosing pulmonary tuberculosis, and five studies (930 participants) compared Xpert Ultra to Xpert MTB/RIF for rifampicin resistance.

How confident are we in the results of this review?

Confident. The review included sufficient studies and participants and used optimum reference standards. In the comparison between Xpert Ultra and Xpert MTB/RIF, most studies were at low risk of bias.

Who do the results of this review apply to?

People considered to have pulmonary tuberculosis.

What are the implications of this review?

The results of these studies indicate that, in theory, for a population of 1000 people where 100 of those presenting with symptoms have pulmonary tuberculosis, Xpert Ultra will miss 9 cases, and Xpert MTB/RIF will miss 15 cases. The number of people wrongly diagnosed with pulmonary tuberculosis would be 40 with Xpert Ultra, and 14 with Xpert MTB/RIF.

The results of these studies indicate that, in theory, for a population of 1000 people where 100 of those have rifampicin resistance, Xpert Ultra will miss 5 cases, and Xpert MTB/RIF will miss 5 cases. The number of people wrongly diagnosed with rifampicin resistance would be 8 with Xpert Ultra, and 11 with Xpert MTB/RIF.

How up-to-date is this review?

28 January 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Xpert Ultra versus Xpert MTB/RIF for the detection of pulmonary tuberculosis*

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

Patients/population: adults with presumptive pulmonary tuberculosis. Participants were unselected, meaning they were not enrolled in a study based on microscopy smear results or history of tuberculosis

Role: an initial test

Index tests: Xpert Ultra and Xpert MTB/RIF

Threshold for index tests: an automated result is provided

Reference standards: solid or liquid culture

Studies: cross-sectional and cohort studies

Setting: primary care facilities and local hospitals

Xpert Ultra sensitivity 90.9% (86.2 to 94.7) and specificity 95.6% (93.0 to 97.4)

Xpert MTB/RIF sensitivity 84.7% (78.6 to 89.9) and specificity 98.4% (97.0 to 99.3)

Test result	Number of results per 1000 patients tested (95% CrI)**						Number of participants*** (studies)	Certainty of the evidence (GRADE)
	Prevalence 2.5%		Prevalence 10%		Prevalence 30%			
	Xpert Ultra	Xpert MTB/RIF	Xpert Ultra	Xpert MTB/RIF	Xpert Ultra	Xpert MTB/RIF		
True positives (TP)	**23** (22 to 24)	**21** (20 to 22)	**91** (86 to 95)	**85** (79 to 90)	**273** (259 to 284)	**254** (236 to 270)	983 (7)	⊕⊕⊕⊕ High
	2 more TP in Xpert Ultra		**6 more TP in Xpert Ultra**		**19 more TP in Xpert Ultra**			
False negatives (FN)	**2** (1 to 3)	**4** (3 to 5)	**9** (5 to 14)	**15** (10 to 21)	**27** (16 to 41)	**46** (30 to 64)		
	2 fewer FN in Xpert Ultra		**6 fewer FN in Xpert Ultra**		**19 fewer FN in Xpert Ultra**			
True negatives (TN)	**932** (907 to 950)	**959** (946 to 968)	**860** (837 to 877)	**886** (873 to 894)	**669** (651 to 682)	**689** (679 to 695)	1852 (7)	⊕⊕⊕⊕ High
	27 fewer TN in Xpert Ultra		**26 fewer TN in Xpert Ultra**		**20 fewer TN in Xpert Ultra**			

False positives (FP)	**43** (25 to 68)	**16** (7 to 29)	**40** (23 to 63)	**14** (6 to 27)	**31** (18 to 49)	**11** (5 to 21)
	27 more FP in Xpert Ultra		**26 more FP in Xpert Ultra**		**20 more FP in Xpert Ultra**	

Abbreviations: CrI: credible interval

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.
**95% credible limits were estimated based on those around the point estimates for pooled sensitivity and specificity. Prevalence estimates were suggested by the World Health Organization Global Tuberculosis Programme. The median tuberculosis prevalence in the included studies was 30.1% (range 12.8% to 72.2%).
***In the Xpert Ultra analysis there were 1851 participants. Piersimoni 2019 reported three non-determinate results for Xpert Ultra and two for Xpert MTB/RIF, accounting for the small difference in the total number of participants.

Summary of findings 2. Xpert Ultra versus Xpert MTB/RIF for the detection of rifampicin resistance*

Review question: what is the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for the detection of rifampicin resistance?

Patients/population: adults with presumptive pulmonary tuberculosis

Role: an initial test

Index tests: Xpert Ultra and Xpert MTB/RIF

Threshold for index tests: an automated result is provided

Reference standards: drug susceptibility testing, line probe assay

Studies: cross-sectional and cohort studies

Setting: primary care facilities and local hospitals

Xpert Ultra sensitivity 94.9% (88.9 to 97.9) and specificity 99.1% (97.7 to 99.8)

Xpert MTB/RIF sensitivity 95.3% (90.0 to 98.1) and specificity 98.8% (97.2 to 99.6)

Test result	Number of results per 1000 patients tested (95% CrI)**			Number of participants*** (studies)	Certainty of the evidence (GRADE)
	Prevalence 2%	Prevalence 10%	Prevalence 15%		

	Xpert Ultra	**Xpert MTB/RIF**	**Xpert Ultra**	**Xpert MTB/RIF**	**Xpert Ultra**	**Xpert MTB/RIF**		
True positives (TP)	**19** (18 to 20)	**19** (18 to 20)	**95** (89 to 98)	**95** (90 to 98)	**142** (133 to 147)	**143** (135 to 147)	238 (5)	⊕⊕⊕⊕ High
	0 fewer TP in Xpert Ultra		**0 fewer TP in Xpert Ultra**		**1 fewer TP in Xpert Ultra**			
False negatives (FN)	**1** (0 to 2)	**1** (0 to 2)	**5** (2 to 11)	**5** (2 to 10)	**8** (3 to 18)	**7** (3 to 15)		
	0 fewer FN in Xpert Ultra		**0 fewer FN in Xpert Ultra**		**1 more FN in Xpert Ultra**			
True negatives (TN)	**971** (957 to 977)	**968** (953 to 976)	**892** (879 to 897)	**889** (875 to 896)	**842** (830 to 847)	**840** (826 to 847)	692 (5)	⊕⊕⊕⊕ High
	3 more TN in Xpert Ultra		**3 more TN in Xpert Ultra**		**2 more TN in Xpert Ultra**			
False positive (FP)	**9** (3 to 23)	**12** (4 to 27)	**8** (3 to 21)	**11** (4 to 25)	**8** (3 to 20)	**10** (3 to 24)		
	3 fewer FP in Xpert Ultra		**3 fewer FP in Xpert Ultra**		**2 fewer FP in Xpert Ultra**			

Abbreviations: CrI: credible interval

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 results of the individual included studies contributing to each summary test accuracy measure.
**Prevalence estimates were suggested by the World Health Organization Global Tuberculosis Programme. The median prevalence of rifampicin resistance in the included studies was 23.6% (range 1.9% to 31.8%). Credible limits were estimated based on those around the point estimates for pooled sensitivity and specificity.
***Xpert Ultra included 921 participants, and Xpert MTB/RIF included 930 participants, mainly owing to indeterminate results with Xpert Ultra.

BACKGROUND

Tuberculosis is a leading cause of infectious disease-related death and is one of the top 10 causes of death worldwide (WHO Global tuberculosis report 2020). In 2019, 10 million people developed tuberculosis disease, a number that over the past several years has been decreasing slowly (WHO Global tuberculosis report 2020). Of the 10 million tuberculosis cases, approximately 8% occurred among people living with HIV. When tuberculosis is detected early and effectively treated, the disease is largely curable. However, in 2019, around 1.2 million HIV-negative people and 208,000 HIV-positive people died from tuberculosis (WHO Global tuberculosis report 2020). The World Health Organization (WHO) estimates that, from 2000 to 2019, more than 60 million lives were saved by diagnosing and treating tuberculosis. The COVID-19 pandemic threatens to reverse the gains made in recent years. A modelling study by the WHO suggests that there could have been between 200,000 and 400,000 additional tuberculosis deaths in 2020 if, over a period of three months, 25% to 50% fewer people were detected with and treated for tuberculosis (WHO Global tuberculosis report 2020).

Drug-resistant tuberculosis is a serious threat to global health. For the purpose of surveillance and treatment, drug-resistant tuberculosis is classified as rifampicin-resistant tuberculosis, multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant tuberculosis (XDR-TB). MDR-TB is defined as resistance to at least isoniazid and rifampicin, the two most important first-line antituberculosis drugs. XDR-TB is defined as MDR-TB plus resistance to at least one drug in the fluoroquinolone class and one of the second-line injectable agents. In 2019, there were approximately half a million new cases of rifampicin-resistant tuberculosis (of which 78% had MDR-TB) worldwide, with India (27%), China (14%), and the Russian Federation (9%) accounting for the largest burden, and 12,350 cases of XDR-TB (WHO Global tuberculosis report 2020). Globally in 2019, 59% of bacteriologically confirmed new cases were tested for rifampicin resistance, an increase from 51% in 2018 (WHO Global tuberculosis report 2020).

In 2014, the World Health Assembly unanimously approved the WHO End TB Strategy, a 20-year strategy devised to end the global tuberculosis epidemic (WHO 2015a). Early diagnosis of tuberculosis, including universal drug susceptibility testing and systematic screening of contacts and high-risk groups, is a key part of the strategy.

The same or similar text appears in the Background and Methods sections in related protocols and reviews (Kay 2020; Kohli 2021; Shapiro 2020; Vonasek 2020).

Target condition being diagnosed

Pulmonary tuberculosis

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis (M tuberculosis)* and is spread from person to person through the air (CDC 2020). 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.

Rifampicin resistance

Rifampicin inhibits bacterial DNA-dependent ribonucleic acid (RNA) polymerase, encoded by the RNA polymerase gene (*rpoB*) (Hartmann 1967). Resistance to this drug has mainly been associated with mutations in a limited region of the *rpoB* gene (Telenti 1993). Rifampicin resistance may occur alone or in association with resistance to isoniazid and other drugs. In high MDR-TB settings, the presence of rifampicin resistance alone may serve as a proxy for MDR-TB (WHO 2011a). People with drug-resistant tuberculosis can transmit the infection to others. The drugs used to treat MDR-TB are less potent and more toxic than the drugs used to treat drug-susceptible tuberculosis, historically requiring two years or more of therapy. The WHO has issued recommendations that all individuals with MDR-TB or rifampicin-resistant tuberculosis, including those who are also resistant to fluoroquinolones, may benefit from effective all-oral treatment regimens (WHO Consolidated Guidelines (Module 4) 2020).

Index test(s)

Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra, the newest version of Xpert MTB/RIF) (Cepheid Inc, Sunnyvale, USA) are the index tests. The index tests are nucleic acid amplification tests (NAAT; i.e. molecular tests) used for diagnosing tuberculosis and rifampicin-resistant tuberculosis. Xpert MTB/RIF and Xpert Ultra cartridges are used with the GeneXpert system (Cepheid 2018; Cepheid 2019). Xpert MTB/RIF and Xpert Ultra are able to detect both *M tuberculosis* complex and rifampicin resistance within two hours after starting the test, with minimal hands-on technical time. With Xpert MTB/RIF and Xpert Ultra, unlike in conventional NAAT, sample processing and polymerase chain reaction (PCR) amplification and detection are integrated into a single, self-enclosed test unit, the GeneXpert cartridge. Following sample loading, all steps in the assay are completely automated and self-contained. In addition, the assays' 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). Except as described below for Ultra trace call results, a single Xpert MTB/RIF or Xpert Ultra run will provide both detection of tuberculosis and detection of rifampicin resistance. One cannot deselect testing for rifampicin resistance and only run the assay for tuberculosis detection.

The development of Xpert MTB/RIF was a major step toward improving detection of tuberculosis and rifampicin resistance globally (Boehme 2010; Small 2011). Since Xpert MTB/RIF was released, there have been four generations (G1, G2, G3, and G4) of the test involving different software and cartridge combinations. Although in comparison with smear microscopy, Xpert MTB/RIF has increased sensitivity for pulmonary tuberculosis (Steingart 2014), the test has suboptimal sensitivity in people with smear-negative and HIV-associated tuberculosis. A Cochrane Review on the diagnostic accuracy of Xpert MTB/RIF for pulmonary tuberculosis found pooled sensitivity and specificity (95% credible interval (CrI)) of 85% (82 to 88) and 98% (97 to 98) (70 studies, 37,237 unselected participants; high-certainty evidence) (Horne 2019). However, Xpert MTB/RIF sensitivity was decreased in people with smear-negative culture-positive disease, pooled sensitivity of

67% (62 to 72), and people living with HIV, pooled sensitivity of 81% (75 to 86) (Horne 2019). Xpert MTB/RIF versions have also had some limitations in detecting rifampicin resistance.

In order to overcome these limitations, Cepheid developed Xpert Ultra, a re-engineered assay using a newly developed cartridge that is run on the same device after a software upgrade. To improve sensitivity for tuberculosis detection, Xpert Ultra incorporates two different multi-copy amplification targets and a larger DNA reaction chamber than Xpert MTB/RIF (WHO 2017). A laboratory study reported that the limit of detection (the lowest number of colony-forming units (CFUs) per sample that can be reproducibly distinguished from negative samples with 95% confidence) using Xpert Ultra improved to 15.6 CFU/mL of sputum compared to 112.6 CFU/mL for Xpert MTB/RIF (Chakravorty 2017).

Importantly, Xpert Ultra added a new semiquantitative category for tuberculosis detection that was not present in Xpert MTB/RIF: "trace call" corresponds to the lowest bacillary load for *M tuberculosis* detection (WHO 2017). This new category is reported as MTB trace DETECTED. No rifampicin resistance results are available (reported as INDETERMINATE) for people with trace results. As with Xpert MTB/RIF, Xpert Ultra detects both live and dead bacteria.

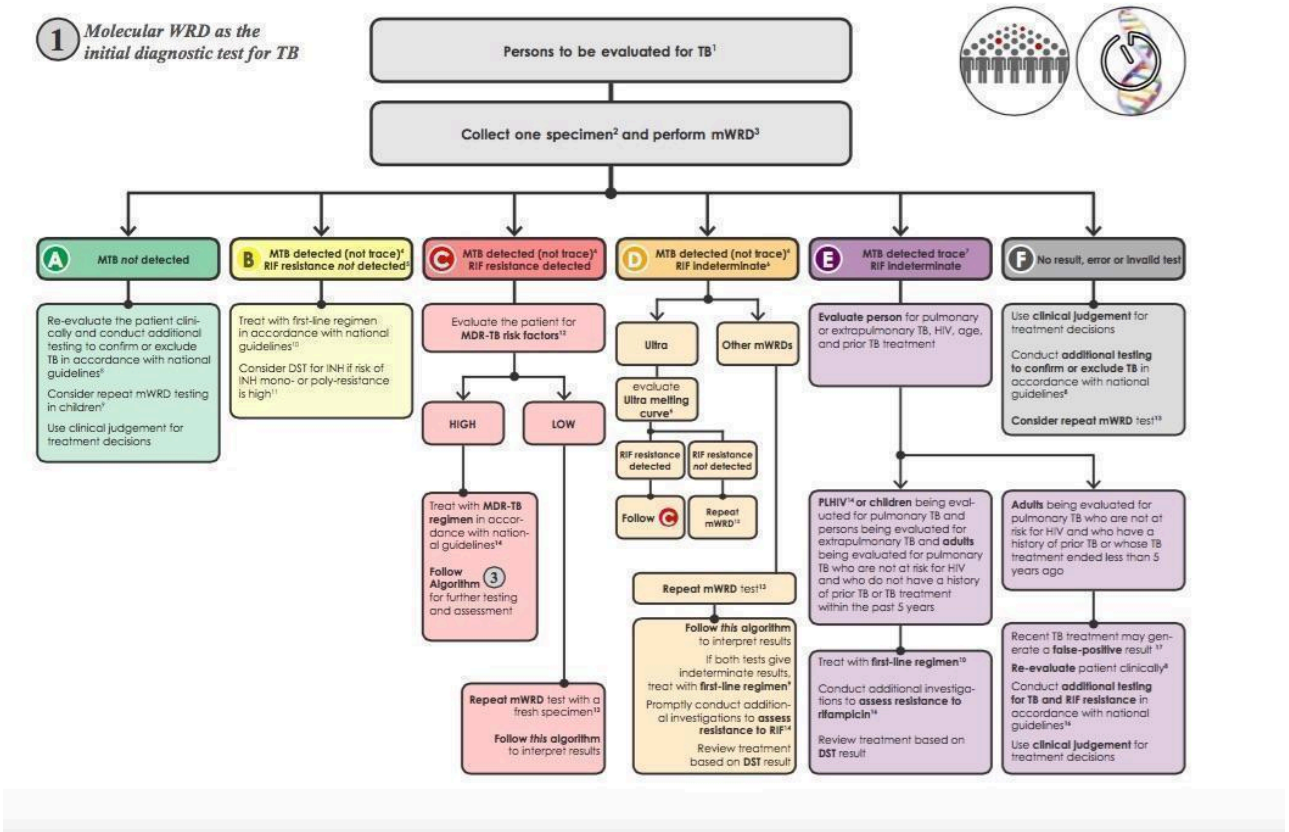
To address limitations in rifampicin resistance detection, Xpert Ultra uses melting temperature-based analysis, in lieu of real-time PCR analysis with Xpert MTB/RIF. Melting temperature-based analysis allows Xpert Ultra to better distinguish resistance-conferring mutations from silent mutations (Global Laboratory Initiative 2017).

The test procedure may be used directly on clinical specimens, either raw sputum specimens or sputum pellets created after decontaminating and concentrating the sputum (Blakemore 2010). In both cases, the test material is combined with the assay sample reagent (sodium hydroxide and isopropanol), mixed by hand or vortex, and incubated at room temperature for 15 minutes. The reagent:sample volume ratio is 2:1 for unprocessed sputum and 3:1 for sputum pellets. After the incubation step, 2 mL of the treated specimen are transferred to the cartridge and the run is initiated. The manufacturer does not specifically mention the use of the index tests with frozen specimens (Cepheid 2018; Cepheid 2019). As with Xpert MTB/RIF, Xpert Ultra using the GeneXpert system requires an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules (Global Laboratory Initiative 2019). Like previous Xpert cartridge generations, Xpert Ultra can be performed by operators with minimal technical expertise (Theron 2014b). The time to run the assay is shorter for Xpert Ultra (65 to 87 minutes) than for Xpert MTB/RIF (112 minutes) (Global Laboratory Initiative 2017).

Clinical pathway

Xpert Ultra and Xpert MTB/RIF are used for the diagnosis of tuberculosis and rifampicin resistance. Figure 1 shows the clinical pathway and presents the context in which the index tests might be used. The target condition is pulmonary tuberculosis. Individuals to be evaluated for pulmonary tuberculosis are adults with signs or symptoms suggestive of tuberculosis, such as cough, fever, night sweats, weight loss, haemoptysis, and fatigue, or with an abnormal chest x-ray suggestive of tuberculosis. Additionally, people who are known to have tuberculosis and are at risk for rifampicin-resistant tuberculosis or MDR-TB (e.g. those with a previous history of tuberculosis treatment or those who have an inadequate response to antituberculosis treatment) may undergo Xpert Ultra testing to evaluate for rifampicin resistance.

Figure 1. The clinical pathway describes how people might present and the point in the pathway at which they would be considered for testing with Xpert MTB/RIF or Xpert Ultra. Abbreviations: DST: drug susceptibility testing; INH: isoniazid; MDR-TB: multidrug-resistant tuberculosis; MTB: *Mycobacterium tuberculosis*; mWRD: molecular WHO-recommended rapid diagnostic; PLHIV: people living with HIV; RIF: rifampicin; TB: tuberculosis; Ultra: Xpert Ultra; WHO: World Health Organization. [1]Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB, or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the diagnosis of extrapulmonary TB using CSF, lymph node and other tissue specimens.
[2]Programs may consider collecting two specimens upfront. The first specimen should be promptly tested using the molecular WRD test. The second specimen may be used for the additional testing described in this algorithm. For persons being evaluated for pulmonary TB, sputum is the preferred specimen. Tissue biopsy samples are difficult or impossible to obtain repeatedly; therefore, they should be tested with as many methods as possible (e.g. molecular WRD, culture, DST or histology).
[3]Molecular WRD tests appropriate for this algorithm include Xpert MTB/RIF, Xpert Ultra, Truenat MTB, Truenat MTB Plus and TB-LAMP.
[4]"MTB detected (not trace)" includes MTB detected as high, moderate, low or very low. These categories apply to the original Xpert MTB/RIF and Xpert Ultra tests. Results of the Truenat MTB and MTB Plus tests and the TB-LAMP test also fall into the category of "MTB detected (not trace)". Additional footnotes are explained in WHO Consolidated Guidelines (Module 4) 2020. This algorithm for the use of a molecular WHO-recommended rapid diagnostic (WRD), which includes Xpert Ultra and Xpert MTB/RIF, comes from the WHO operational handbook on tuberculosis (WHO Consolidated Guidelines (Module 4) 2020). Copyright © [2020] [World Health Organization]: reproduced with permission.



The downstream consequences of testing include the following.

- True-positive (TP): patients would benefit from rapid diagnosis and appropriate treatment.
- True-negative (TN): patients would be spared unnecessary treatment and would benefit from reassurance and pursuit of an alternative diagnosis.

- 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.
- False-negative (FN): increased risk of morbidity and mortality and delayed treatment initiation; risk of ongoing tuberculosis transmission.

Settings of interest

We were interested in how the index tests performed in people with presumptive pulmonary tuberculosis, who were evaluated as they would be in routine practice, most often in local hospitals or primary care centres. The index tests may have the greatest impact on health when used in a setting such as a primary healthcare facility, where treatment can be started the same day as testing or as soon as possible.

Role of index test(s)

We were interested in the following roles for testing.

I. Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis

Index test used as an initial test replacing smear microscopy and culture for the diagnosis of pulmonary tuberculosis in adults with presumptive pulmonary tuberculosis (WHO Consolidated Guidelines (Module 3) 2020). An initial test does not mean that other tests will follow.

II. Xpert Ultra and Xpert MTB/RIF for the detection of rifampicin resistance

Index test used as an initial test replacing culture and phenotypic drug susceptibility testing for the diagnosis of rifampicin-resistant tuberculosis in adults with presumptive pulmonary tuberculosis (WHO Consolidated Guidelines (Module 3) 2020).

As mentioned, in high MDR-TB settings the presence of rifampicin resistance alone may serve as a proxy for MDR-TB. Xpert Ultra and Xpert MTB/RIF do not eliminate the need for subsequent culture and phenotypic drug susceptibility testing (DST), which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin, respectively.

Alternative test(s)

In this section, we describe selected alternative tests for the detection of pulmonary tuberculosis and rifampicin resistance. For a comprehensive review of alternative tests, we refer the reader to several excellent resources (Branigan 2019; Lewinsohn 2017; Unitaid 2017).

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. Advantages of smear microscopy include its simplicity, low cost, speed, and high specificity in high tuberculosis burden areas. In addition, smear microscopy identifies the most infectious people with tuberculosis. Smear microscopy can be performed in basic laboratories. Drawbacks of smear microscopy include the need for specialized training and its relatively low sensitivity, 50% to 60% on average for a direct smear (Steingart 2006b). Around 5000 to 10,000 organisms per millilitre must be present in the specimen for tuberculosis bacteria to be visible by microscopy (American Thoracic Society 2000). Although the sensitivity of microscopy can be improved by approximately 10% with fluorescence (Steingart 2006a), a large number of tuberculosis cases will still go undiagnosed. Smear-negative tuberculosis is disproportionately higher in HIV-positive than in HIV-negative individuals, accounting for 24% to 61% of all pulmonary cases in people living with HIV (Getahun 2007; Perkins 2007). Microscopy cannot distinguish between drug-susceptible tuberculosis and drug-resistant tuberculosis. The WHO recommends that microscopy as the initial diagnostic test be replaced with WHO-recommended rapid tests that can simultaneously detect tuberculosis and tuberculosis drug resistance (WHO Consolidated Guidelines (Module 3) 2020).

Mycobacterial culture is a method used to grow bacteria on nutrient-rich media. In comparison with microscopy, a positive culture requires only around 100 organisms per millilitre, and therefore can detect lower numbers of tuberculosis bacteria (American Thoracic Society 2000). Additionally, culture is essential for species identification and DST. However, culture is a relatively complex and slow procedure. Solid culture typically takes between four to eight weeks for results, and liquid culture, although more sensitive and rapid than solid culture, requires up to six weeks and is more prone to contamination (WHO 2015b). In addition, culture requires specialized laboratories and highly skilled staff. Culture is the reference standard for pulmonary tuberculosis in this review.

NAAT are molecular systems that can detect small quantities of genetic material (DNA or RNA) from microorganisms, such as *M tuberculosis*. The key advantage of NAAT is that they are rapid diagnostic tests, potentially providing results in a few hours. A variety of molecular amplification methods are available, of which PCR is the most common. NAAT are available as commercial kits and in-house tests (based on a protocol developed in a laboratory) and are routinely used in high-income countries for tuberculosis detection. In-house PCR is widely used in low-income countries because these tests are less expensive than commercial kits. However, in-house PCR is known to produce inconsistent results (Flores 2005). In addition to Xpert MTB/RIF and Xpert Ultra, the WHO recommends Truenat tuberculosis technology (Truenat MTB, MTB Plus and MTB-RIF Dx assays) (Molbio Diagnostics, Goa, India) to detect tuberculosis and rifampicin-resistant tuberculosis (WHO Consolidated Guidelines (Module 3) 2020).

Alternative molecular methods for DST 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 (Nathavitharana 2017). MTBDR*plus* is the most widely studied line probe assay. Advantages of line probe assays are that they can provide a result for the 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). The WHO recommends that for individuals with a sputum smear-positive specimen or a cultured tuberculosis isolate, commercial molecular line probe assays may be used as the initial test instead of phenotypic culture-

based DST to detect resistance to rifampicin and isoniazid (WHO Consolidated Guidelines (Module 3) 2020). Other molecular assays for the detection of tuberculosis and resistance to rifampicin and isoniazid are in development (Walzl 2018).

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. This urine test has potential advantages over sputum-based testing due to the ease of sample collection. The accuracy of urinary LAM detection is improved among people living with HIV with advanced immunosuppression (Bjerrum 2019). The use of AlereLAM in HIV-positive adult inpatients was shown to reduce mortality in two randomized trials (Gupta-Wright 2018; Peter 2016). Based on evidence from the randomized trials and a Cochrane Review (Bjerrum 2019), the WHO currently recommends that AlereLAM be used to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children (WHO Consolidated Guidelines (Module 3) 2020). The key change from the WHO 2015 guidelines is broadening the indication for the use of lateral flow LAM among HIV-positive inpatients with signs and symptoms of active tuberculosis (pulmonary and extrapulmonary); the test is now recommended for all such patients, irrespective of their CD4 count (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% confidence interval 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).

Rationale

Xpert Ultra and Xpert MTB/RIF are rapid tests that may provide benefits for patients (earlier diagnosis and the opportunity to begin earlier, appropriate treatment) and for public health (opportunities to interrupt tuberculosis transmission), especially in high tuberculosis burden countries.

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 (strong recommendation, moderate-certainty evidence) (WHO 2011b). 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-[certainty] evidence) (WHO 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 to second-line drugs) remains essential to detect resistance to drugs other than rifampicin (WHO 2013). In 2017, based on a non-inferiority analysis of Xpert Ultra compared with Xpert MTB/RIF, 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 2017).

In December 2019, the WHO convened a Guideline Development Group to update the recommendations on the use of molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance. To extend the work of our previous Cochrane Review (Horne 2019), we performed this review update to inform updates to WHO policy (WHO Consolidated Guidelines (Module 3) 2020).

OBJECTIVES

Primary objectives

To compare the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis and detection of rifampicin resistance in adults with presumptive pulmonary tuberculosis.

Secondary objectives

For detection of pulmonary tuberculosis, to investigate the effects of potential sources of heterogeneity such as smear status, HIV status, and history of tuberculosis on test accuracy.

For detection of rifampicin resistance, to investigate the effect of smear status (smear positive and smear negative) on test accuracy.

To summarize the frequency of Xpert Ultra trace-positive results.

To estimate the accuracy of Xpert Ultra after repeat testing in those with trace-positive results.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional and cohort type diagnostic accuracy studies that directly compared the index tests in participants with presumptive pulmonary tuberculosis. These study designs included paired and randomized comparative accuracy studies. Paired comparative accuracy studies are those in which each participant receives both index tests. Randomized comparative accuracy studies are those which randomly allocate participants to index tests, with each participant receiving only one index test. 'Presumptive pulmonary tuberculosis' refers to a patient who presents with symptoms or signs suggestive of tuberculosis. We included studies where the index tests were evaluated for both pulmonary tuberculosis and rifampicin resistance, pulmonary tuberculosis alone, or rifampicin resistance alone. We also included randomized controlled trials that evaluated the use of the index(s) test on patient health outcomes, but that also reported sensitivity and specificity. Although the study design was a randomized trial for the purpose of determining the impact of the test on participant outcomes, the study design was a cross-sectional study for the purpose of determining the diagnostic accuracy of the index tests in this review. However, we did not identify any randomized controlled trials. We used abstracts to identify published studies

and included these publications if 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 that evaluated the index tests in HIV-positive people irrespective of tuberculosis symptoms, for example HIV-positive people being assessed for antiretroviral therapy. We included these studies for the following reasons: 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; and many HIV-positive people in low-income countries develop tuberculosis as the first manifestation of AIDS.

We excluded case reports and studies with a case-control design, the latter because these types of studies are prone to bias, particularly studies enrolling participants with severe disease and healthy participants without disease. We excluded studies of the index tests in people with diabetes but without tuberculosis symptoms, and studies designed to find people with active tuberculosis in community settings. We excluded drug resistance surveys.

Participants

We included studies that enrolled adults, aged 15 years or older, with presumptive pulmonary tuberculosis, rifampicin-resistant tuberculosis, or MDR-TB. For tuberculosis detection, we were interested in people who were not currently on tuberculosis treatment or those on treatment for less than seven days. Tuberculosis treatment might interfere with the confirmation of tuberculosis on culture (the reference standard for this review). If the treatment status of the participants was unclear, we contacted primary study authors for this information.

We included studies that assessed the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF using sputum and other respiratory specimens, such as fluid obtained from bronchial alveolar lavage and tracheal aspiration, consistent with the intended use of the manufacturer (Cepheid 2018), and studies from all types of health facilities and all laboratory levels (peripheral, intermediate, and central) from all countries. We excluded studies where the age of the participants was unknown.

Index tests

The index tests were Xpert Ultra and Xpert MTB/RIF.

Index 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 Ultra

- 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)

We considered a trace result to mean MTB (*M tuberculosis*) DETECTED.

Xpert MTB/RIF

- 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

Target conditions

The target conditions were active pulmonary tuberculosis and rifampicin resistance.

Reference standards

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

- Pulmonary tuberculosis present was defined as a positive *M tuberculosis* culture.
- Pulmonary tuberculosis absent was defined as a negative *M tuberculosis* culture.

We also included a composite reference standard. The diagnosis of pulmonary tuberculosis was defined as a positive culture or clinical criteria specified by the primary study authors. Clinical criteria might include cough longer than two weeks, fever, night sweats, or weight loss and radiographic findings consistent with pulmonary tuberculosis.

- Pulmonary tuberculosis present was defined as a positive *M tuberculosis* culture or meeting composite reference standard criteria.
- Pulmonary tuberculosis absent was defined as a negative *M tuberculosis* culture and not meeting composite reference standard criteria.

For rifampicin resistance, the reference standards were culture-based drug susceptibility testing (DST), and line probe assays

(LPA) (WHO Consolidated Guidelines (Module 3) 2020). Acceptable methods for DST are 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).

- Rifampicin resistance present was defined as a positive culture-based DST (or LPA) result for resistance.
- Rifampicin resistance absent was defined as a negative culture-based DST (or LPA) result for resistance (i.e. rifampicin susceptible).

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 11 October 2018, 23 August 2019, and 28 January 2020, using the search terms and strategy described in Appendix 1:

Cochrane Infectious Diseases Group Specialized Register; MEDLINE (Ovid, from 1966); Embase (Ovid, from 1974); Science Citation Index - Expanded (from 1900), Conference Proceedings Citation Index - Science (CPCI-S, from 1990), and BIOSIS Previews (from 1926); all three from the Web of Science; Scopus (Elsevier, from 1970); Latin American Caribbean Health Sciences Literature database (LILACS) (BIREME, from 1982). We also searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch), and the ISRCTN registry (www.isrctn.com/) for trials in progress, and ProQuest Dissertations & Theses A&I (from 1990) for dissertations.

In order to identify other systematic reviews and meta-analyses, we performed additional searches on 28 May 2020 in MEDLINE (PubMed), Embase (Ovid), and the Cochrane Library, applying filters for systematic reviews (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) to search terms for Xpert and tuberculosis.

Searching other resources

We reviewed the reference lists of included articles and any relevant review articles identified through the above methods. We also contacted researchers at the Foundation for Innovative New Diagnostics (FIND), the WHO Global Tuberculosis Programme, 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 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 assessed the full-text articles for inclusion using predefined inclusion and exclusion criteria, resolving any discrepancies by discussion with a third review author. We recorded all studies excluded after full-text assessment and their reasons for exclusion in the Characteristics of excluded studies table. We illustrated the study selection process in a PRISMA diagram (Moher 2009). We included search results from the original review and re-evaluated previously included studies to determine if the studies met the refined inclusion criteria.

Data extraction and management

We extracted data on the following characteristics (Appendix 2).

- Author, publication year, study design, country where the study was located, level of laboratory services, clinical setting (outpatient, inpatient, or both outpatient and inpatient), and whether the test was run at point of care
- Population characteristics: age, gender, smear status, HIV status
- Index test(s), Xpert Ultra and Xpert MTB/RIF
- Reference standard
- Condition of the specimen (fresh or frozen)
- Quality Assessment of Studies of Diagnostic Accuracy - Revised (QUADAS-2) items, Whiting 2011, and QUADAS-C, Yang B 2020
- Number of TP, FP, FN, TN (i.e. true positives, false positives, false negatives, true negatives) and trace results
- Number of non-determinate results for the detection of pulmonary tuberculosis
- Number of indeterminate results for the 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 WHO post-2015 era classification (WHO Global tuberculosis report 2020). A country could be classified as high burden for one, two, or all three of the high-burden categories.

Although the manufacturer recommends use of fresh specimens, several studies used frozen specimens, so we also extracted this information. We investigated the influence of condition of specimen in a sensitivity analysis.

Regarding the definition of smear positivity, as most of the included studies performed the index tests in intermediate-level or central-level laboratories, we assumed that these studies adhered to the revised definition of a new sputum smear-positive pulmonary tuberculosis case based on the presence of at least one acid-fast bacillus in at least one sputum sample in countries with a well-functioning external quality assurance system (WHO 2007).

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 Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the quality of the included studies (Whiting 2011). QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. We assessed all domains for risk of bias and the first three domains for concerns regarding applicability. Two review authors, working

independently, completed QUADAS-2, resolving any disagreements through discussion. We have presented the results of this quality assessment in text, tables, and graphs. In addition, we used QUADAS-C (C stands for comparison) to assess risk of bias in the included studies. QUADAS-C was designed to be an extension to QUADAS-2, with a set of additional questions. QUADAS-C results in separate 'Risk of bias' judgements for comparative accuracy studies. QUADAS-C assesses risk of bias in the same four domains as QUADAS-2: (1) patient selection, (2) index tests, (3) reference standard, and (4) flow and timing, but does not assess applicability concerns. The version of QUADAS-C used in this review (v2019.10.10) is a preliminary version which may be revised further (Yang B 2020). QUADAS-2 and QUADAS-C tools tailored to this review are described in Appendix 3.

Statistical analysis and data synthesis

We performed descriptive analyses for the results of the included studies using Stata 15 (Stata 2017). 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). Whenever possible, we included nontuberculous mycobacteria (NTM) as non-tuberculosis for specificity determinations. We chose to use data that were not subject to discrepant analyses (unresolved data) owing to the potential for bias (Hadgu 2005).

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 performed analyses separately by reference standard. Whenever possible, we determined pooled 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 allowed us to calculate the pooled estimates of sensitivity and specificity while dealing with potential sources of variation caused by (1) imprecision of sensitivity and specificity estimates within individual studies; (2) correlation between sensitivity and specificity across studies; and (3) variation in sensitivity and specificity between studies. For Xpert Ultra and Xpert MTB/RIF for detection of pulmonary tuberculosis among smear-positive individuals (described below), we performed a univariate analysis. For the primary analysis of Xpert Ultra versus Xpert MTB/RIF for tuberculosis detection, we estimated accuracy using studies that did not preselect participants based on prior microscopy testing or that primarily included participants with a history of tuberculosis. In addition, we determined predictive values at a pretest probability of 10%, a value suggested by the WHO.

Rifampicin resistance detection

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

- were culture-positive;
- had a valid phenotypic DST or LPA result;
- were Xpert Ultra or Xpert MTB/RIF tuberculosis-positive; and
- had a valid Xpert Ultra or Xpert MTB/RIF result for rifampicin resistance, detected or not detected (susceptible).

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

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

Comparison of Xpert Ultra and Xpert MTB/RIF

We performed meta-analyses of the accuracy of Xpert Ultra and Xpert MTB/RIF in studies that made direct comparisons between Xpert Ultra versus Xpert MTB/RIF (Takwoingi 2013). We extracted the median and the 95% credible interval (CrI) for all parameters of interest from samples of the posterior distributions. The 95% CrI is the Bayesian equivalent of the classical (frequentist) 95% confidence interval (CI). We compared the accuracy of Xpert Ultra versus Xpert MTB/RIF by estimating the difference in their pooled sensitivities and the difference in their pooled specificities and calculated the probability that Xpert Ultra accuracy exceeds (or is less than) that of Xpert MTB/RIF accuracy.

We estimated all models using a Bayesian approach with low-information prior distributions using OpenBUGS software (Version 3.2.3) (Lunn 2009) and R (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. We summarize the model and the OpenBUGS program we used to implement it in the Statistical Appendix (Appendix 4). As meta-analysis models may be sensitive to the choice of prior distributions over between-study standard deviation parameters, we performed sensitivity analyses using alternative prior distributions that are less informative, allowing a wider range of possible values. We noted no appreciable change in pooled accuracy parameters but, as expected, found that the posterior credible intervals and prediction intervals were slightly wider. Information from the prior distribution is combined with the likelihood of the observed data in accordance with Bayes theorem to obtain a posterior distribution for each unknown parameter (Appendix 5).

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% 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 have 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 plots using R (R Core Team 2019).

Approach to inconclusive index test results

The index tests report an inconclusive test result for unexpected results. The proportion of inconclusive (non-determinate) results for the detection of pulmonary tuberculosis is the number of tests classified as INVALID, ERROR, or NO RESULT divided by the total number of index tests performed. The proportion of inconclusive

(indeterminate) results for the detection of rifampicin resistance is the number of tests classified as MTB DETECTED; RIF (rifampicin) resistance INDETERMINATE divided by the total number of index test-positive results. We used a Bayesian hierarchical model for a single proportion to estimate the pooled proportion of inconclusive tests results. For participants with trace results on Xpert Ultra, rifampicin resistance is always reported as INDETERMINATE. As we found very few inconclusive results reported, we excluded these results from the quantitative analysis and separately reported the pooled proportion of non-determinate and indeterminate index test results. In addition, we compared the pooled proportion (expressed as a percentage) of indeterminate results for Xpert Ultra versus Xpert MTB/RIF by estimating the difference in their pooled proportions with the probability that these differences exceed zero.

Investigations of heterogeneity

We visually inspected forest plots and summary receiver operating characteristics (SROC) plots to explore heterogeneity in the sensitivity and specificity estimates for Xpert Ultra and Xpert MTB/RIF. We performed the following subgroup analyses.

Detection of pulmonary tuberculosis

For the detection of pulmonary tuberculosis, we performed comparative analyses for Xpert Ultra versus Xpert MTB/RIF with respect to smear status (smear negative and smear positive), HIV status (positive and negative), and history of tuberculosis (yes or no). We performed these analyses by fitting a bivariate model to each subgroup. We extracted the median and the 95% CrI for the difference in the pooled sensitivities and the difference in the pooled specificities, respectively, of Xpert Ultra versus Xpert MTB/RIF. When there were at least four studies in a subgroup, we also calculated the probability that the difference exceeds zero in each case.

Among smear-positive individuals, we performed a univariate analysis because in several studies the value for true negatives plus false positives was zero, and specificity was inestimable.

Detection of rifampicin resistance

For the detection of rifampicin resistance, we compared Xpert Ultra and Xpert MTB/RIF accuracy with respect to smear status (smear positive and smear negative).

Xpert Ultra trace results

Summary of Xpert Ultra trace-positive results and repeated testing of Ultra trace specimens

Xpert Ultra added a new result category, trace, that corresponds to the lowest bacillary load for *M tuberculosis* detection (WHO 2017). This new category is reported as MTB trace DETECTED. We summarized the frequency of Xpert Ultra trace-positive results, as well as the frequency of trace results in individuals with a history of tuberculosis. We also summarized the accuracy of Xpert Ultra repeated test for diagnosing pulmonary tuberculosis in people who have an initial Ultra trace result.

Nontuberculous mycobacteria

NTM, such as *M avium* complex and *M abscessus*, constitute a multi-species group of environmental mycobacteria that can cause pulmonary disease in humans that clinically resembles tuberculosis. People living with HIV with severe immunosuppression are particularly vulnerable to infections caused by NTM (Gopinath 2010). Previous studies have shown that Xpert MTB/RIF does not cross-react with other mycobacterial species (Helb 2010). We summarized data for NTM separately by determining the proportion (expressed as a percentage) of false-positive Xpert Ultra and Xpert MTB/RIF results in specimens that grew NTMs.

Sensitivity analyses

For Xpert Ultra for detection of pulmonary tuberculosis, we performed sensitivity analyses by limiting inclusion in the meta-analysis based on the following criteria.

- Studies that included only untreated participants. We excluded studies that did not explicitly state that they included only untreated participants.
- Studies that used liquid culture as the reference standard.
- Studies where a consecutive or random sample of participants was enrolled.
- Studies where the reference standard was blinded.
- Studies that only used fresh specimens.
- Studies that accounted for all participants in the analysis. We excluded studies where we answered no or unclear to the QUADAS-2 flow and timing signalling question: Were all patients included in the analysis?

We did not perform sensitivity analyses for Xpert MTB/RIF, as we performed these analyses in the previous update of this review. Most of these analyses included greater than 50 studies (Horne 2019).

Assessment of reporting bias

We chose not to carry out formal assessments of publication bias using methods such as funnel plots or regression tests, because such techniques have not been helpful for diagnostic test accuracy studies (Macaskill 2010). As Xpert Ultra and Xpert MTB/RIF are produced by only one manufacturer and subjected to considerable scrutiny, we believe that reporting bias was minimal.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach for diagnostic studies (Balshem 2011; Schünemann 2008; Schünemann 2016). As recommended, we rated the certainty of 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) based on five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each outcome, the certainty of evidence started as high when there were high-quality studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty. If there was a reason for downgrading, we used our judgement to classify the reason as either serious (downgraded by one level) or very serious (downgraded by two levels). Two review authors discussed the judgements of the certainty of the evidence and applied GRADE in the following way (GRADEpro GDT; Schünemann 2020a; Schünemann 2020b).

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

- Indirectness: we assessed indirectness in relation to the population (including disease spectrum), setting, interventions, and outcomes (accuracy measures). 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 to investigate potential sources of heterogeneity and did not downgrade when we believed we could 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 asked ourselves, would we make a different decision if the lower or upper boundary of the CrI represented the truth? In addition, we worked out projected ranges for TP, FN, TN, and FP for a given prevalence of tuberculosis and made judgements on imprecision from these calculations.
- Publication bias: we rated publication bias as undetected (not serious). 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.

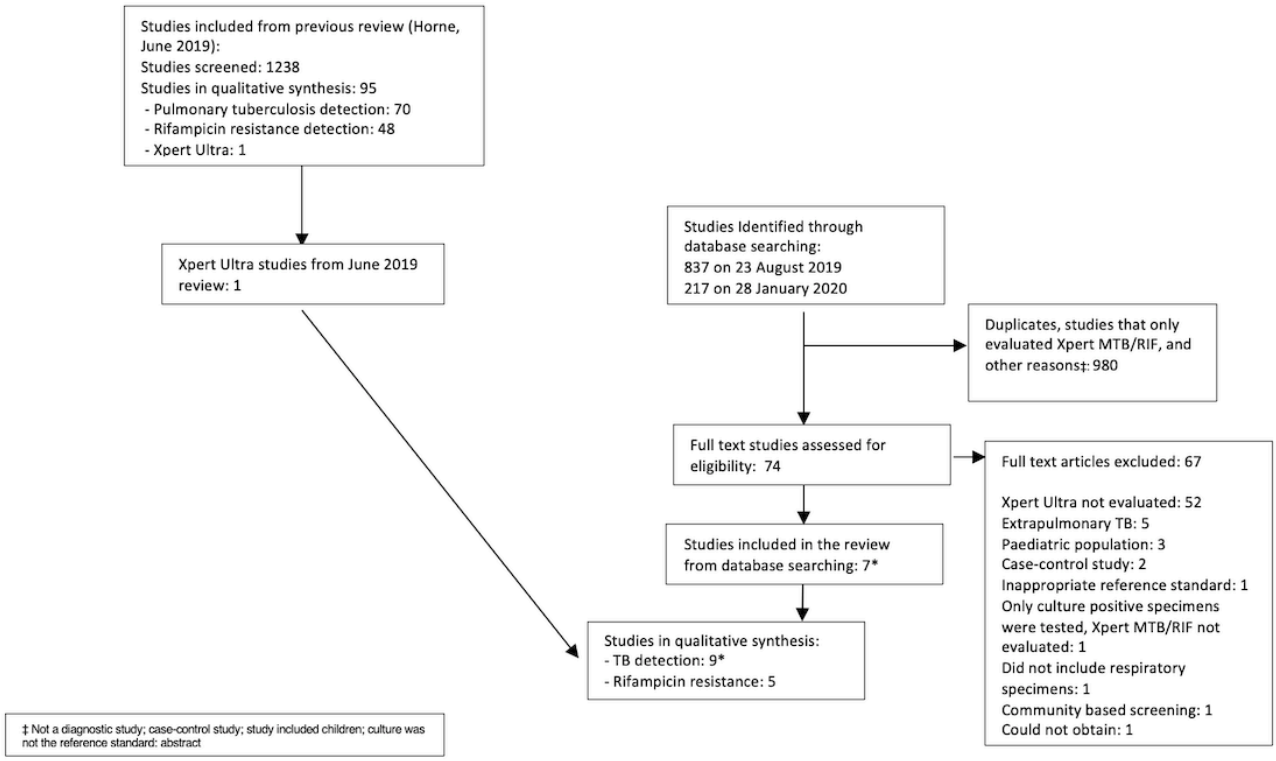
RESULTS

Results of the search

We identified and screened a total of 1054 records for inclusion in this review update. Of these, we assessed 74 full-text papers against our inclusion criteria. We excluded 67 papers for the following reasons: Xpert Ultra not evaluated (n = 52), extrapulmonary tuberculosis (n = 5), paediatric population (n = 3), case-control study (n = 2), inappropriate reference standard (n = 1), only culture-positive specimens were tested and Xpert MTB/RIF not evaluated (n = 1), did not include respiratory specimens (n = 1), community-based screening (n = 1), and could not obtain full text (n = 1).

We identified eight eligible publications including nine unique studies; one publication contributed two distinct cohorts (Mishra 2020a; Mishra 2020b). All included studies compared Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Pereira 2020; Piersimoni 2019; Wang 2019). Of the total nine studies, five studies compared Xpert Ultra and Xpert MTB/RIF for the detection of rifampicin resistance (Chakravorty 2017; Dorman 2018; Mishra 2020b; Piersimoni 2019; Wang 2019). Figure 2 shows the flow of studies in the review. We recorded the excluded studies, including selected studies from the previous Cochrane Review (Horne 2019), and the reasons for their exclusion in the Characteristics of excluded studies table.

Figure 2. PRISMA flow diagram of studies in the review. *One publication contributed two distinct studies, which were classified as Mishra 2020a and Mishra 2020b.



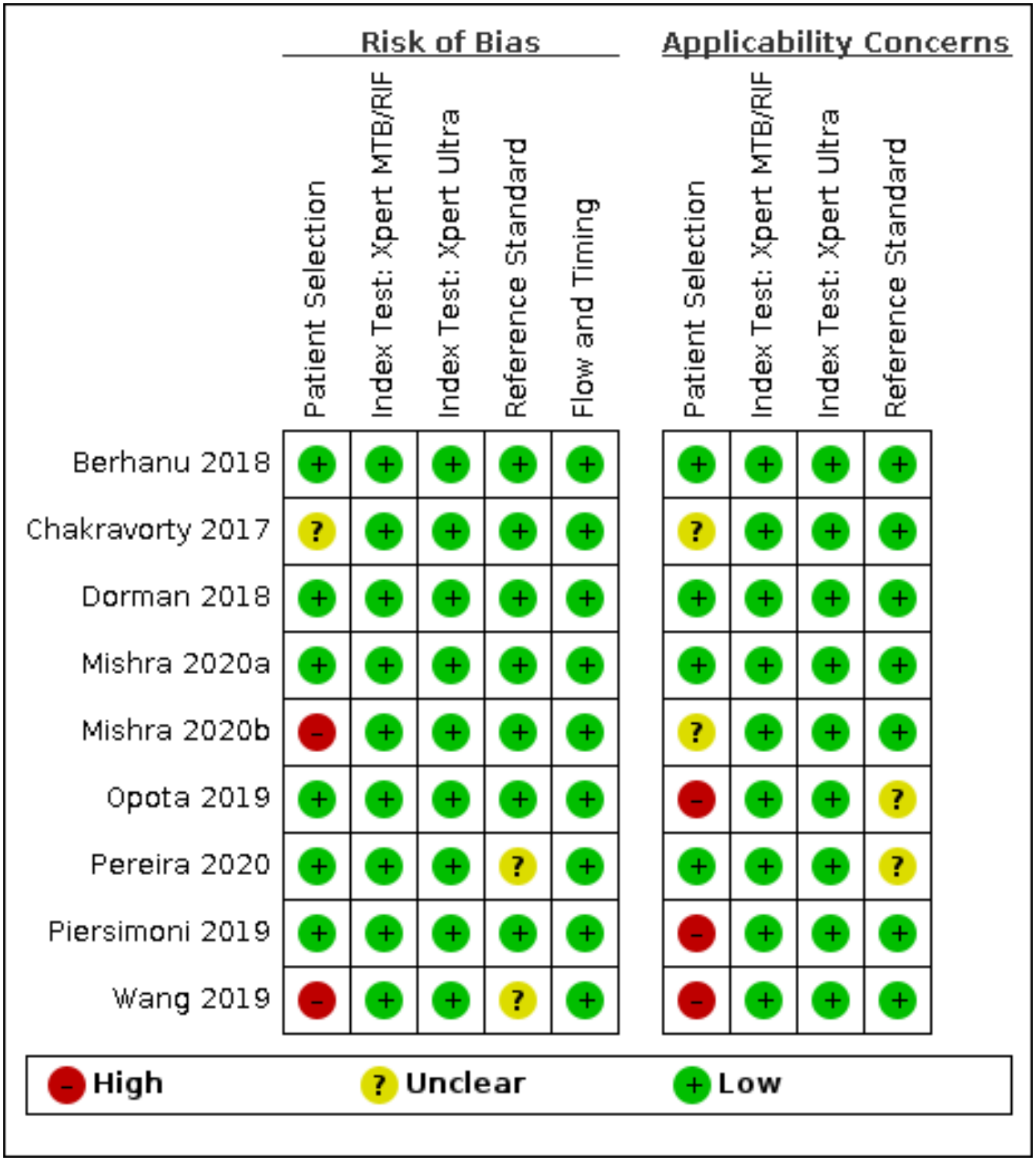
Methodological quality of included studies

Studies evaluating Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis

QUADAS-2

Figure 3 shows the risk of bias and applicability concerns for nine studies evaluating Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis.

Figure 3. Risk of bias and applicability concerns summary for detection of pulmonary tuberculosis: review authors' judgements about each domain for each included study.



In the patient selection domain, we considered six studies (67%) to have low risk of bias because the study enrolled a consecutive or random sample of eligible participants and avoided inappropriate exclusions (Berhanu 2018; Dorman 2018; Mishra 2020a; Opota 2019; Pereira 2020; Piersimoni 2019). We considered two studies (22%) to have high risk of bias: one study exclusively enrolled participants who had recently received tuberculosis treatment (Mishra 2020b), and one study exclusively enrolled smear-negative participants (Wang 2019). We considered one study to have unclear risk of bias because the manner of patient selection was not reported (Chakravorty 2017). With respect to applicability, we considered four studies (44%) to have low concern because participants in these studies were evaluated in primary care facilities, local hospitals, or both settings (Berhanu 2018; Dorman 2018; Mishra 2020a; Pereira 2020). We considered three studies (33%) to have high concern: two studies because participants were evaluated

exclusively as inpatients in tertiary care centres (Piersimoni 2019; Wang 2019), and one study because the setting was a hospital performing a laboratory-based evaluation for the purpose of airborne isolation (Opota 2019). We considered two studies (22%) to have unclear concern because we could not tell (Chakravorty 2017; Mishra 2020b).

In the index test domain, we considered all studies to have low risk of bias because the results of the index tests (Xpert Ultra and Xpert MTB/RIF) are automatically generated. Regarding applicability, we considered all studies to have low concern.

In the reference standard domain, we considered seven studies (78%) to have low risk of bias because the results of the reference standard were interpreted without knowledge of the results of the index test (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Piersimoni 2019). We considered two studies (22%) to have unclear risk of bias because information about blinding was not reported (Pereira 2020; Wang 2019). Regarding applicability, we considered seven studies (78%) to have low concern because these studies performed a test to identify *M tuberculosis* species (speciation) (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Mishra 2020b; Piersimoni 2019; Wang 2019), and two studies (22%) to have unclear concern because we could not tell (Opota 2019; Pereira 2020).

In the flow and timing domain, we considered all studies (100%) to have low risk of bias because all participants were included in the analysis.

QUADAS-C

Appendix 6 shows risk of bias for nine studies comparing Xpert Ultra and Xpert MTB/RIF. Seven studies used a paired diagnostic accuracy design (Chakravorty 2017; Dorman 2018; Mishra 2020a; Opota 2019; Pereira 2020; Piersimoni 2019; Wang 2019), and two studies used a randomized design (Berhanu 2018; Mishra 2020b).

In the patient selection domain, we considered six studies (78%) to have low risk of bias: in five studies participants were consecutively enrolled (Dorman 2018; Mishra 2020a; Opota 2019; Pereira 2020; Piersimoni 2019), and in one study participants were randomly enrolled (Berhanu 2018). In Berhanu 2018, all participants received Xpert MTB/RIF, and the order by which participants were selected to receive Xpert Ultra or a third index test (not included in this review) was randomized. We considered three studies (33%) to have high risk of bias: one study did not report the manner of participant selection (Chakravorty 2017); one study exclusively enrolled participants who had recently received tuberculosis treatment (Mishra 2020b); and one study exclusively enrolled smear-negative participants (Wang 2019).

In the index test domain, we judged low risk of bias for all studies**.**

In the reference standard domain, we considered seven studies (78%) to have low risk of bias because the results of the reference standard were interpreted without knowledge of the results of the index test (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Piersimoni 2019). We considered two studies (22%) to have unclear risk of bias because information about blinding was not reported (Pereira 2020; Wang 2019).

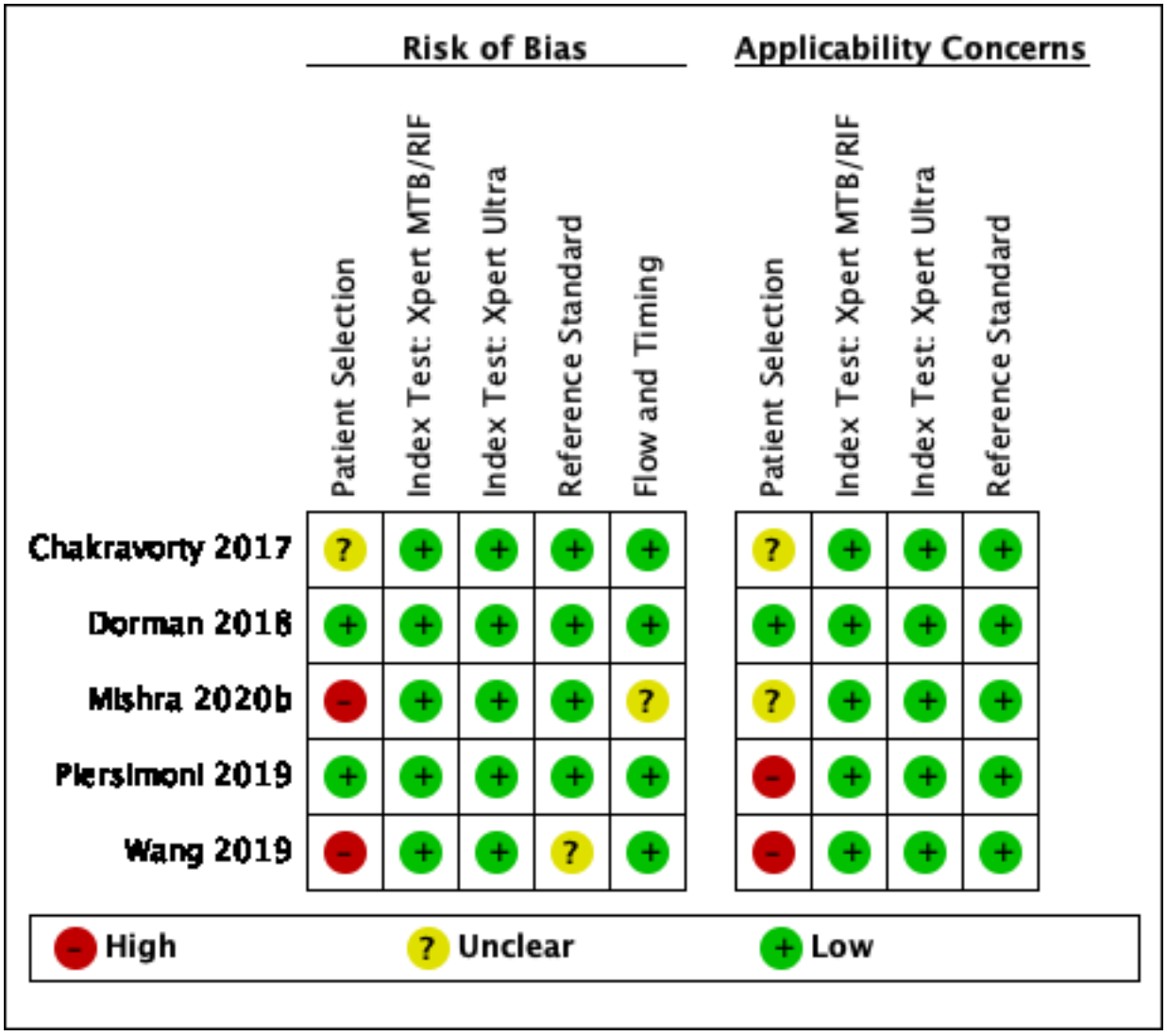
In the flow and timing domain, we judged low risk of bias for all studies**.**

Studies evaluating Xpert Ultra and Xpert MTB/RIF for the detection of rifampicin resistance

QUADAS-2

Figure 4 shows risk of bias and applicability concerns for the five studies evaluating Xpert Ultra and Xpert MTB/RIF for rifampicin resistance detection.

Figure 4. Risk of bias and applicability concerns summary for detection of rifampicin resistance: review authors' judgements about each domain for each included study.



In the patient selection domain, we considered two studies (40%) to have low risk of bias because the studies enrolled a consecutive or random sample of eligible participants and avoided inappropriate exclusions (Dorman 2018; Piersimoni 2019). We considered two studies (40%) to have high risk of bias: one study exclusively enrolled participants who had recently received tuberculosis treatment (Mishra 2020b), and one study preselected participants on the basis of their sputum specimens being paucibacillary (smear-negative) (Wang 2019). We considered one study (20%) to have unclear risk of bias because the manner of participant selection was not reported (Chakravorty 2017). Regarding applicability, we considered one study (20%) to have low concern because participants in this study were evaluated in primary care facilities and local hospitals (Dorman 2018). We considered two studies (40%) to have high concern because participants were evaluated exclusively as inpatients in tertiary care centres (Piersimoni 2019; Wang 2019). We considered the remaining two studies (40%) to have unclear concern because we could not tell (Chakravorty 2017; Mishra 2020b).

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

In the reference standard domain, we considered four studies (80%) to have low risk of bias because the results of the reference standard were interpreted without knowledge of the results of the index test (Chakravorty 2017; Dorman 2018; Mishra 2020b; Piersimoni 2019). We considered one study (20%) to have unclear risk of bias because information on blinding was not reported (Wang 2019). With respect to applicability in the reference standard domain, we considered all studies to have low concern because all specimens had already been speciated and identified as *M tuberculosis* in these studies.

In the flow and timing domain, we considered four studies (80%) to have low risk of bias because all participants were included in

the analysis. We considered one study to have unclear risk of bias because, in comparison to Xpert MTB/RIF, Xpert Ultra had a higher number of rifampicin resistance indeterminate results which were not included in the accuracy estimates (Mishra 2020b).

QUADAS-C

Appendix 7 shows risk of bias for five studies comparing Xpert Ultra and Xpert MTB/RIF. Four studies used a paired diagnostic accuracy design (Chakravorty 2017; Dorman 2018; Piersimoni 2019; Wang 2019), and one study used a randomized design (Mishra 2020b).

In the patient selection domain, we considered two studies (40%) to have low risk of bias (Dorman 2018; Piersimoni 2019); and three studies to have high risk of bias: one study did not report the manner of participant selection (Chakravorty 2017); one study exclusively enrolled participants who had recently received tuberculosis treatment (Mishra 2020b); and one study preselected paucibacillary specimens (Wang 2019).

In the index test domain, we considered all studies (100%) to have low risk of bias.

In the reference standard domain, we considered four studies (80%) to have low risk of bias (Chakravorty 2017; Dorman 2018; Mishra 2020b; Piersimoni 2019), and one study to have unclear risk of bias because information on blinding was not reported (Wang 2019).

In the flow and timing domain, we considered four studies (80%) to have low risk of bias because all participants were included in the analysis (Chakravorty 2017; Dorman 2018; Piersimoni 2019; Wang 2019). We considered one study to have unclear risk of bias because, in comparison with Xpert MTB/RIF, Xpert Ultra had a higher number of rifampicin resistance indeterminate results which were not included in the accuracy estimates (Mishra 2020b).

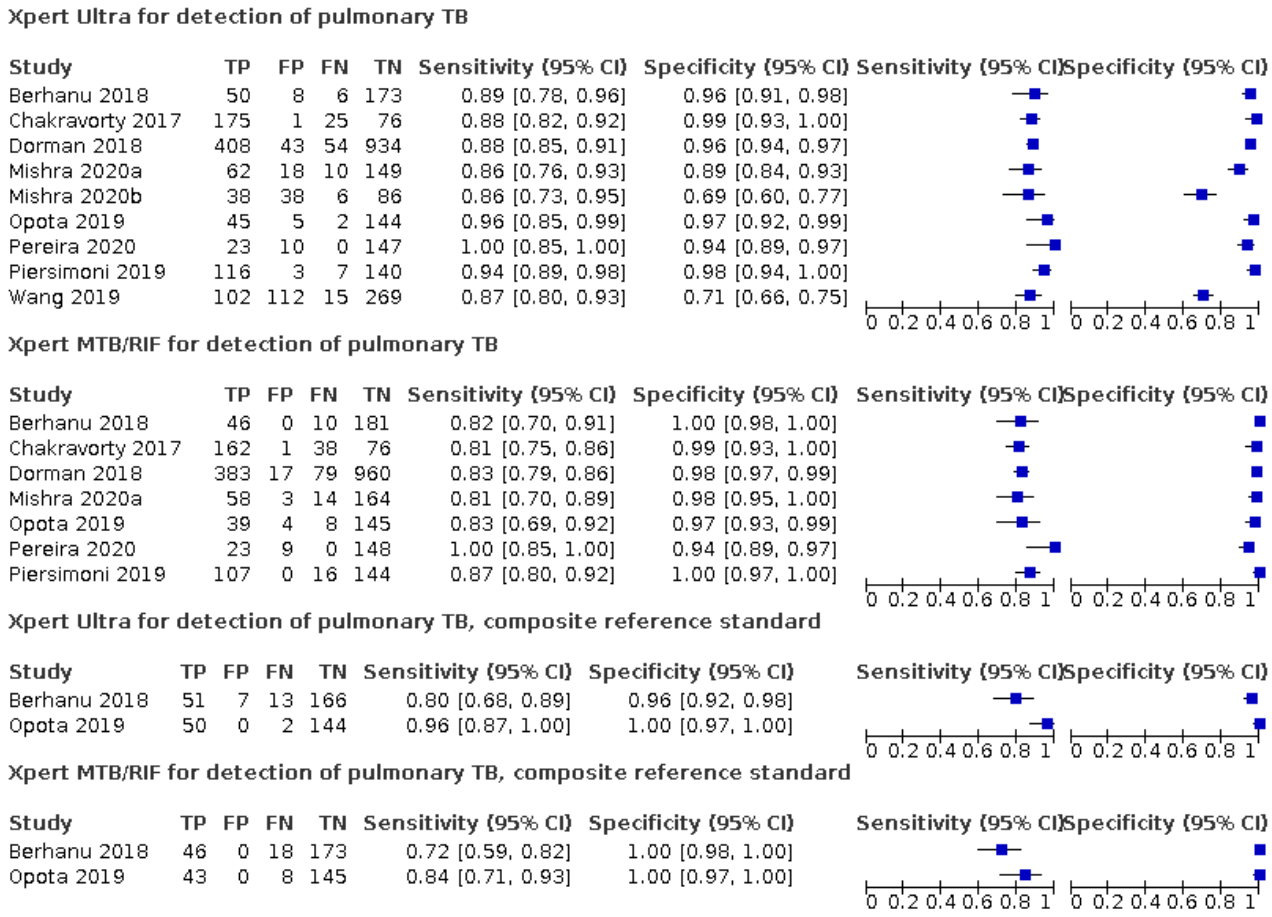
Findings

Of the total nine studies, seven (78%) were conducted in low- or middle-income countries, and seven (78%) were mainly or exclusively conducted in high tuberculosis burden countries. Seven studies (78%) reported the HIV status of participants (Berhanu 2018; Dorman 2018; Mishra 2020a; Mishra 2020b; Pereira 2020; Piersimoni 2019; Wang 2019), which ranged from 0%, Wang 2019, to 62%, Berhanu 2018. Four studies (44%) evaluated only fresh specimens (Berhanu 2018; Dorman 2018; Mishra 2020a; Pereira 2020); two studies (22%) evaluated only archived frozen samples (Mishra 2020b; Piersimoni 2019); and three studies (33%) evaluated both fresh and frozen specimens (Chakravorty 2017; Opota 2019; Wang 2019). For the culture reference standard, one study used only solid culture (Pereira 2020); five studies (56%) used only liquid culture (Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Piersimoni 2019); and three studies (33%) used both solid and liquid cultures (Berhanu 2018; Chakravorty 2017; Wang 2019). Key characteristics of the included studies are described in the Characteristics of included studies table and Table 1.

I. Xpert Ultra versus Xpert MTB/RIF for the detection of pulmonary tuberculosis

We identified seven studies that compared Xpert Ultra and Xpert MTB/RIF in unselected participants against culture (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Opota 2019; Pereira 2020; Piersimoni 2019). The median sample size was 239 (interquartile range (IQR) 217 to 272). The prevalence of pulmonary tuberculosis in the studies ranged from 12.8% to 72.2%. The sensitivity of Xpert Ultra ranged from 86% to 100%, and the sensitivity of Xpert MTB/RIF from 81% to 100%. The specificity of Xpert Ultra ranged from 89% to 99%, and the specificity of Xpert MTB/RIF from 94% to 100% (Figure 5).

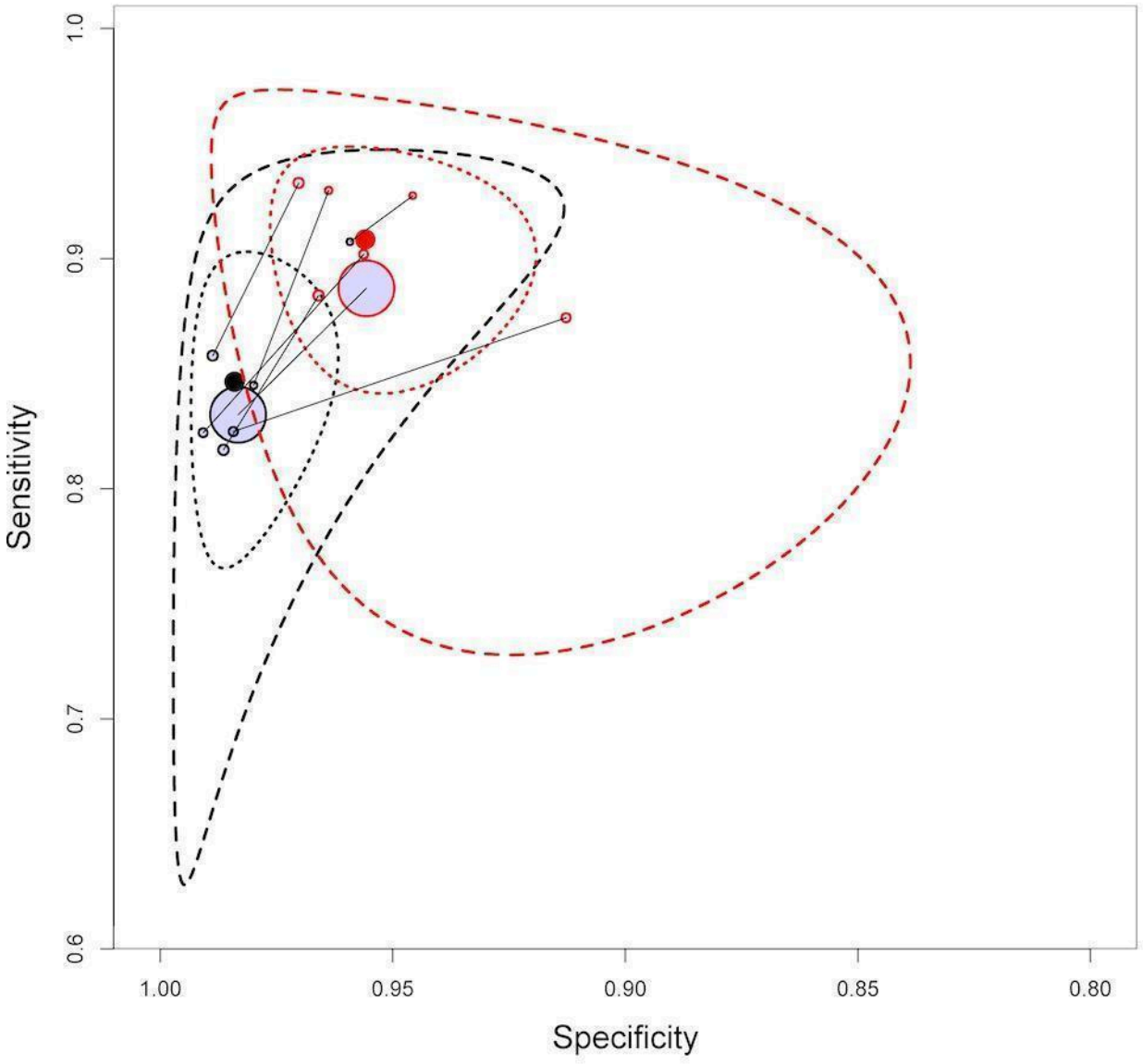
Figure 5. Forest plots of Xpert Ultra versus Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in adults, unselected participants by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



Xpert Ultra pooled sensitivity and specificity (95% CrI) were 90.9% (86.2 to 94.7) and 95.6% (93.0 to 97.4) (2834 participants, 983 (34.7%) with tuberculosis); Xpert MTB/RIF pooled sensitivity and specificity were 84.7% (78.6 to 89.9) and 98.4% (97.0 to 99.3) (2835 participants, 983 (34.7%) with tuberculosis) (Table 2). Piersimoni 2019 reported three non-determinate results for Xpert Ultra and two for Xpert MTB/RIF, accounting for the small difference in the total number of participants in this analysis. The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at 6.3% (0.1 to 12.8) for sensitivity and −2.7% (−5.7 to −0.5) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.98. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 0.99 (Table 3).

Figure 6 presents the SROC plot for Xpert Ultra and Xpert MTB/RIF pooled sensitivity and specificity estimates together with the credible and prediction regions for pulmonary tuberculosis. The summary point (pooled value) appears close to the upper left-hand corner of the plots, suggesting high accuracy of both Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis. The 95% credible regions around the summary points of sensitivity and specificity, the regions that contain likely combinations of the pooled sensitivity and specificity, are relatively narrow. The 95% prediction region is slightly wider for Xpert Ultra, displaying more uncertainty as to where the likely values of sensitivity and specificity might occur in a future study.

Figure 6. Summary plot of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for the detection of pulmonary tuberculosis. 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, Xpert Ultra (red) and Xpert MTB/RIF (black). The dotted 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 receiver operator characteristic (ROC) space where data have been observed.



We identified two studies that compared the accuracy of Xpert Ultra and Xpert MTB/RIF against a composite reference standard based on clinical and radiographic findings. In Berhanu 2018, Xpert Ultra sensitivity and specificity (95% CI) were 80% (68 to 89) and 96% (92 to 98) versus Xpert MTB/RIF sensitivity and specificity of 72% (59 to 82) and 100% (98 to 100). In Opota 2019, Xpert Ultra sensitivity and specificity (95% CI) were 96% (87 to 100) and 100% (97 to 100) versus Xpert MTB/RIF sensitivity and specificity of 84% (71 to 93) and 100% (97 to 100) (Figure 5).

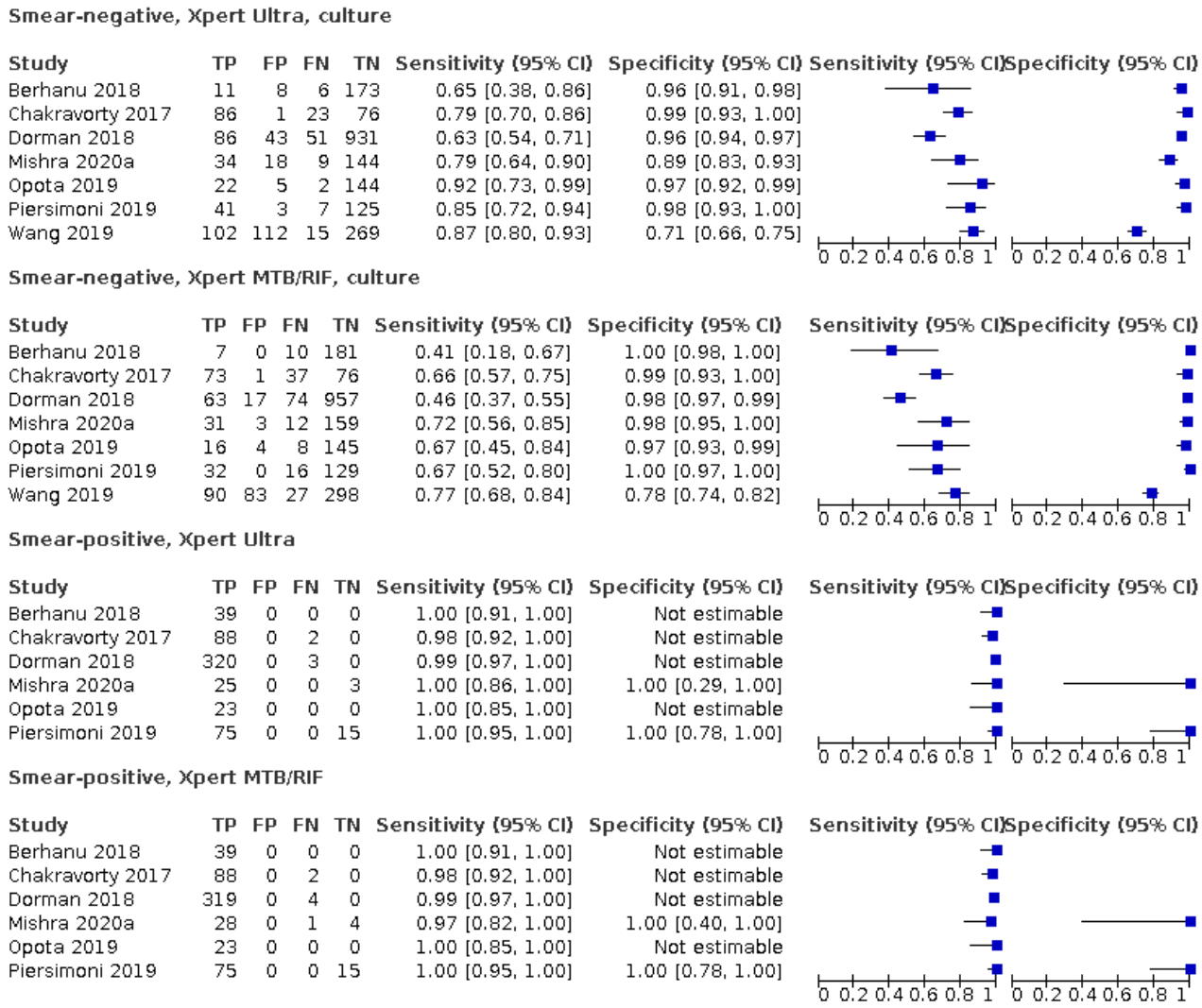
Subgroup analyses

The results of the subgroup analyses by smear status, HIV status, and history of tuberculosis are shown in Table 3.

Xpert Ultra versus Xpert MTB/RIF in participants with smear-negative sputum specimens

Seven studies reported data for participants with smear-negative specimens (Figure 7) (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Opota 2019; Piersimoni 2019; Wang 2019). The sensitivity of Xpert Ultra ranged from 63% to 92%, and the sensitivity of Xpert MTB/RIF from 41% to 77%. The lowest sensitivity for Xpert Ultra (63%) was reported by Dorman 2018. This was a multicentre study which took place in Belarus, Brazil, China, Georgia, India, Kenya, South Africa, and Uganda, and assessed Xpert Ultra accuracy based on a reference standard of multiple cultures. The lowest sensitivity for Xpert MTB/RIF (41%) was reported by Berhanu 2018. In this study, which took place in South Africa, 62% of participants were HIV-positive. The specificity of Xpert Ultra ranged from 71% to 99%. The lowest specificity for Ultra (71%) was reported by Wang 2019, which preselected smear-negative participants based on prior microscopy testing. The specificity of Xpert MTB/RIF ranged from 78% to 100%, and the lowest specificity (78%) was again reported by Wang 2019.

Figure 7. Forest plots of Xpert Ultra versus Xpert MTB/RIF sensitivity and specificity for the detection of pulmonary tuberculosis by smear status. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



In a meta-analysis of studies with unselected participants (excluding Wang 2019), Xpert Ultra pooled sensitivity was 77.5% (67.6 to 85.6) and pooled specificity was 95.8% (92.9 to 97.7) (6 studies, 2049 participants). Xpert MTB/RIF pooled sensitivity and specificity were 60.6% (48.4 to 71.7) and 98.8% (97.7 to 99.5) (6 studies, 2051 participants). The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at 16.7% (2.1 to 31.8) for sensitivity and −3.0% (−5.9 to −0.9) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.99. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 1.00.

Repeating the meta-analysis including Wang 2019, Xpert Ultra pooled sensitivity was slightly higher at 79.4% (70.2 to 87.0) and specificity (95% CrI) slightly lower at 94.2% (88.3 to 97.5) (7 studies, 2547 participants); Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 63.0% (51.7 to 73.0) and 98.2% (94.9 to 99.6) (7 studies, 2549 participants).

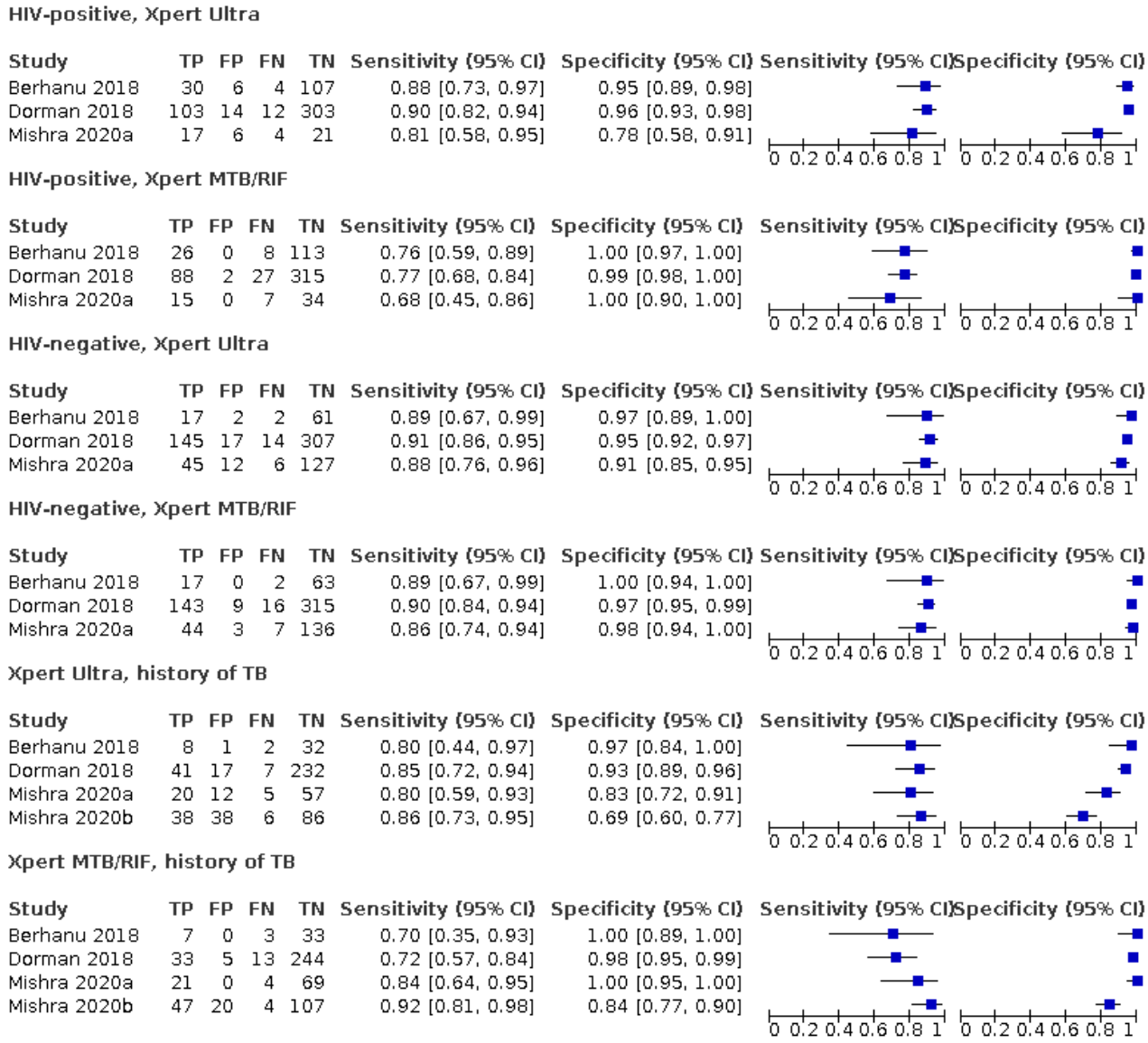
Xpert Ultra versus Xpert MTB/RIF in participants with smear-positive sputum specimens

Six studies reported data for participants with smear-positive specimens (Figure 7) (Berhanu 2018; Chakravorty 2017; Dorman 2018; Mishra 2020a; Opota 2019; Piersimoni 2019). For both index tests, sensitivity estimates were 97% or greater in all studies. For smear-positive pulmonary tuberculosis, Xpert Ultra pooled sensitivity (95% CrI) was 99.3% (98.1 to 99.8) (6 studies, 593 participants); Xpert MTB/RIF pooled sensitivity (95% CrI) was 98.9% (97.5 to 99.6) (6 studies, 598 participants) (Table 3). We did not determine pooled specificity because in four studies the value for true negatives plus false positives was zero, and specificity was not estimable (Berhanu 2018; Chakravorty 2017; Dorman 2018; Opota 2019). The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at 0.3% (−1.0 to 1.8) for sensitivity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.72.

Xpert Ultra versus Xpert MTB/RIF in people living with HIV

Three studies reported data in people living with HIV (Berhanu 2018; Dorman 2018; Mishra 2020a). The sensitivity of Xpert Ultra ranged from 81% to 90%, and the sensitivity of Xpert MTB/RIF from 68% to 77%. The specificity of Xpert Ultra ranged from 78% to 96%; the specificity of Xpert MTB/RIF was higher, ranging from 99% to 100% (Figure 8). Xpert Ultra pooled sensitivity and specificity (95% CrI) were 87.6% (75.4 to 94.1) and 92.8% (82.3 to 97.0) (627 participants); Xpert MTB/RIF pooled sensitivity and specificity were 74.9% (58.7 to 86.2) and 99.7% (98.6 to 100.0) (635 participants) (Table 4).

Figure 8. Forest plots of Xpert Ultra versus Xpert MTB/RIF sensitivity and specificity for the detection of pulmonary tuberculosis by HIV status and history of tuberculosis. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



Xpert Ultra versus Xpert MTB/RIF in HIV-negative people

Three studies reported data for HIV-negative people (Berhanu 2018; Dorman 2018; Mishra 2020a). The sensitivity of Xpert Ultra ranged from 88% to 91%, and the sensitivity of Xpert MTB/RIF from 86% to 90%. The specificity of Xpert Ultra ranged from 91% to 97%; the specificity of Xpert MTB/RIF was higher, ranging from 97% to 100% (Figure 8). Xpert Ultra pooled sensitivity and specificity (95% CrI) were 90.3% (80.3 to 95.6) and 94.3% (79.8 to 98.7) (755 participants); Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 89.0% (78.3 to 94.8) and 98.1% (95.3 to 99.4) (755 participants) (Table 4).

Xpert Ultra versus Xpert MTB/RIF in people with a history of tuberculosis

Four studies reported data for people with a history of tuberculosis (Berhanu 2018; Dorman 2018; Mishra 2020a; Mishra 2020b). The sensitivity of Xpert Ultra ranged from 80% to 86%, and the sensitivity of Xpert MTB/RIF from 70% to 92%. The specificity of Xpert Ultra ranged from 69% to 97%, and the specificity of Xpert MTB/RIF from 84% to 100% (Figure 8). The lowest specificity (69% for Xpert Ultra) was reported by Mishra 2020b, which was notable for preselecting patients who had previously received antituberculosis treatment within the last two years. Xpert Ultra pooled sensitivity and specificity (95% CrI) were 84.2% (72.5 to

91.7) and 88.2% (70.5 to 96.6) (602 participants). Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) were 81.8% (68.7 to 90.0) and 97.4% (91.7 to 99.5) (610 participants). The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at 2.4% (−11.9 to 17.2) for sensitivity and −8.9% (−27.0 to 0.6) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.64. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 0.97.

Repeating the meta-analysis excluding Mishra 2020b, Xpert Ultra pooled sensitivity decreased to 83.3% (66.9 to 92.7), and specificity increased to 91.5% (81.3 to 96.7) (3 studies, 434 participants). Xpert MTB/RIF pooled sensitivity decreased to 76.6% (58.6 to 88.8), and specificity increased to 99.0% (97.7 to 99.8) (3 studies, 432 participants).

Non-determinate results, detection of pulmonary tuberculosis

Regarding Xpert Ultra, six studies reported non-determinate results for tuberculosis detection: 14/253 (5.5%) Mishra 2020a; 64/2001 (3.2%) Dorman 2018; 5/173 (2.9%) Mishra 2020b; 3/269 (1.1%) Piersimoni 2019; 5/503 (1.0%) Wang 2019; 0/237 (0%) Berhanu 2018. Among six studies involving 3436 tests, the pooled proportion of non-determinate test results for Xpert Ultra was low, at 2.0% (0.9 to 3.6).

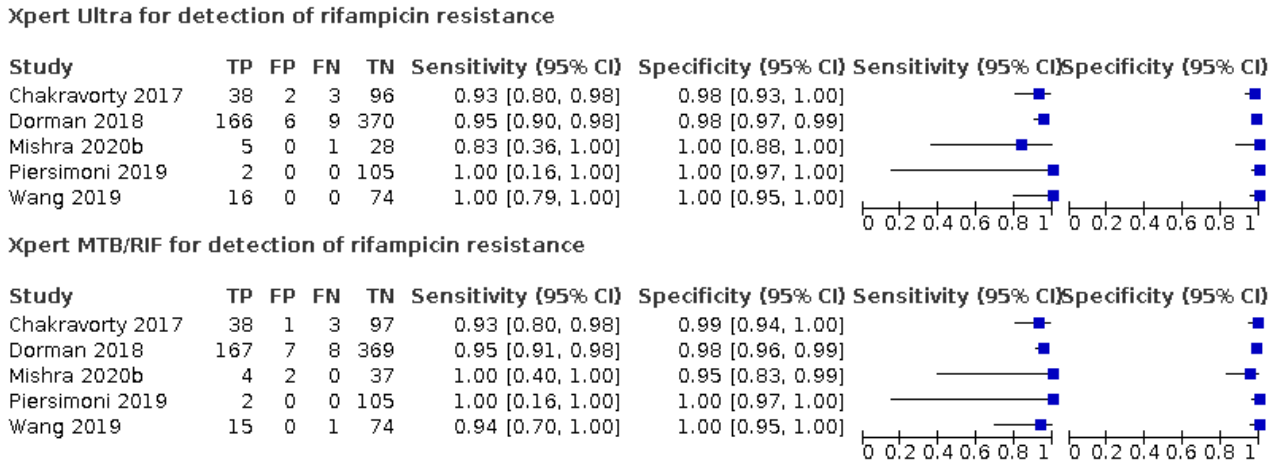
Regarding Xpert MTB/RIF, five studies reported non-determinate results for tuberculosis detection: 14/301 (4.6%) Mishra 2020a; 14/811 (1.7%) Wang 2019; 28/2001 (1.4%) Dorman 2018; 2/269 (0.7%) Piersimoni 2019; 1/179 (0.6%) Mishra 2020b. Among five studies involving 3561 tests, the pooled proportion of non-determinate test results for Xpert MTB/RIF was low, at 1.6% (0.8 to 3.0).

II. Detection of rifampicin resistance

Xpert Ultra versus Xpert MTB/RIF for the detection of rifampicin resistance

We identified five studies that compared Xpert Ultra and Xpert MTB/RIF accuracy for the detection of rifampicin resistance (Chakravorty 2017; Dorman 2018; Mishra 2020b; Piersimoni 2019; Wang 2019). The median sample size was 107 (IQR 90 to 139). The prevalence of rifampicin resistance in the studies ranged from 1.9% to 31.8%. The sensitivity of Xpert Ultra ranged from 83% to 100%, and the sensitivity of Xpert MTB/RIF from 93% to 100%. The specificity of Xpert Ultra ranged from 98% to 100%, and the specificity of Xpert MTB/RIF from 95% to 100% (Figure 9).

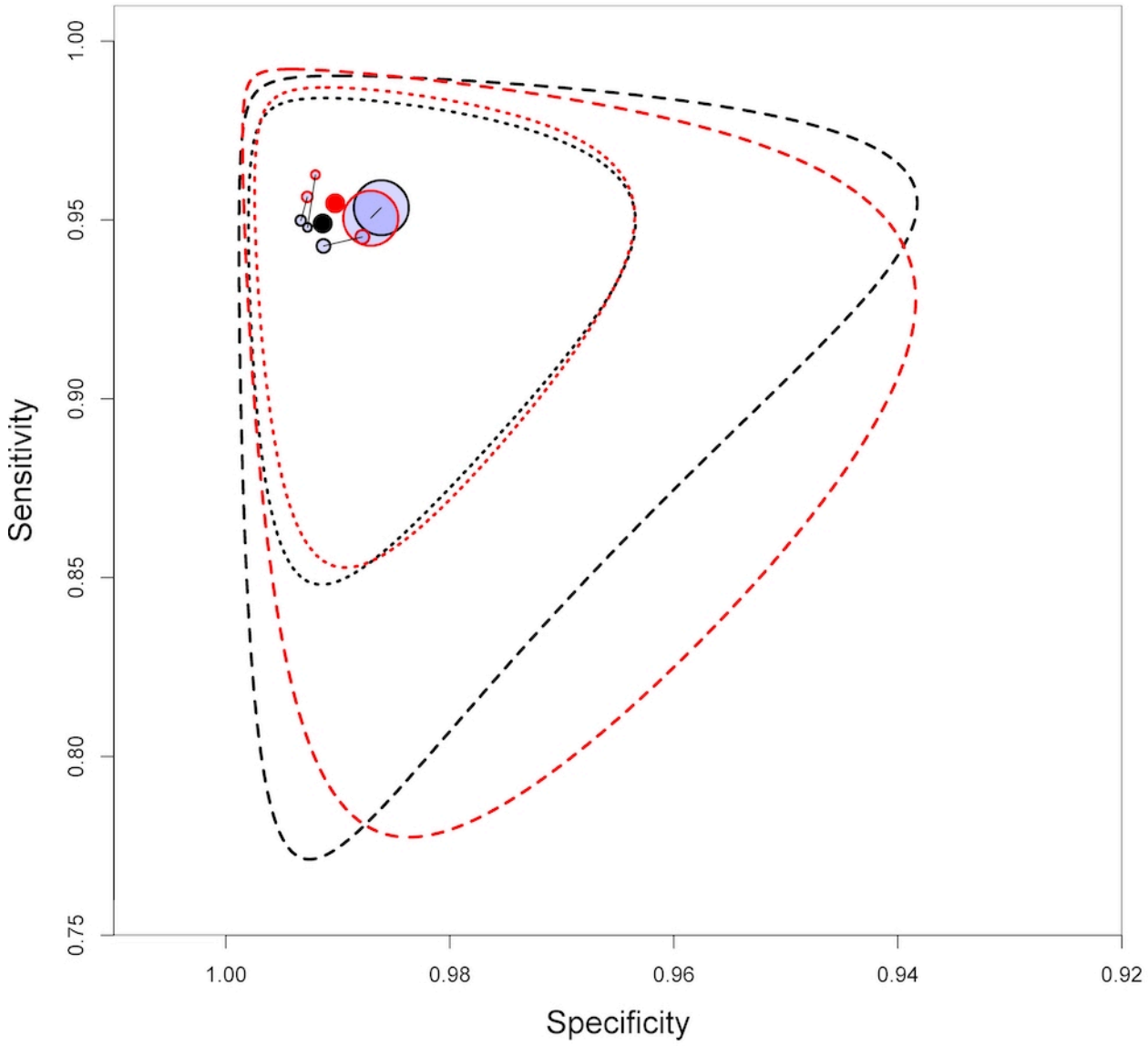
Figure 9. Forest plot of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for the detection of rifampicin resistance. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



Xpert Ultra pooled sensitivity and specificity were 94.9% (88.9 to 97.9) and 99.1% (97.7 to 99.8) (5 studies, 921 participants; high-certainty evidence) versus Xpert MTB/RIF pooled sensitivity and specificity of 95.3% (90.0 to 98.1) and 98.8% (97.2 to 99.6) (5 studies, 930 participants; high-certainty evidence) (Table 2). The pooled sensitivity and specificity estimates for Xpert Ultra and Xpert MTB/RIF were similar. The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at −0.3% (−6.9 to 5.7) for sensitivity and 0.3% (−1.2 to 2.0) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.45. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 0.33.

Figure 10 presents Xpert Ultra and Xpert MTB/RIF pooled sensitivity and specificity estimates together with the credible and prediction regions for rifampicin resistance. The summary point (pooled value) appears close to the upper left-hand corner of the plots, suggesting high accuracy of both Xpert Ultra and Xpert MTB/RIF for the detection of rifampicin resistance. The 95% confidence regions around the summary points of sensitivity and specificity, the regions that contain likely combinations of the pooled sensitivity and specificity, are relatively narrow. The 95% prediction regions, the regions that contain the likely values of sensitivity and specificity in a future study, are also relatively narrow.

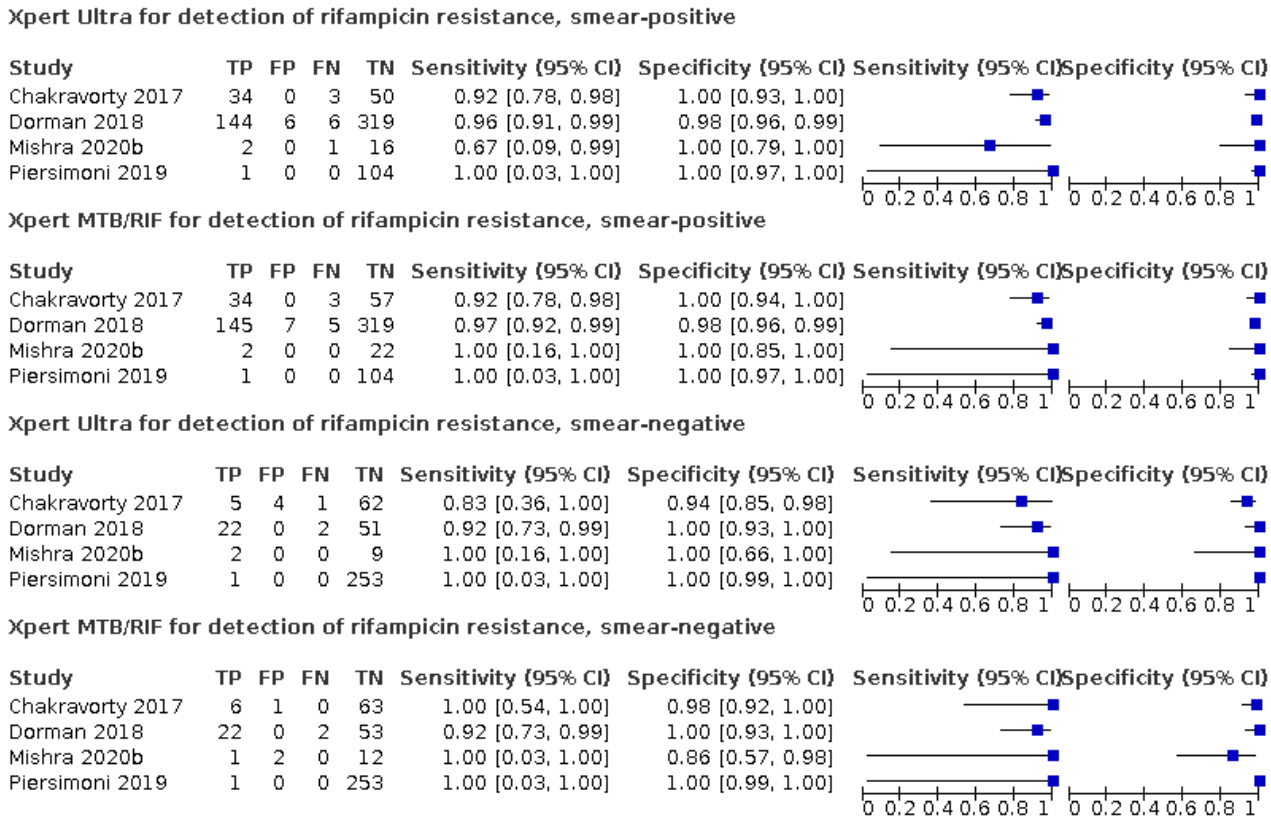
Figure 10. Summary plot of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for the detection of rifampicin resistance. Each individual study is represented by a shaded circle. The size of the circle is proportional to the sample size of the study such that larger studies are represented by larger circles. The filled circle is the median pooled estimate for sensitivity and specificity, Xpert Ultra (red) and Xpert MTB/RIF (black). The dotted 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 receiver operator characteristic (ROC) space where data have been observed.



Xpert Ultra versus Xpert MTB/RIF accuracy for the detection of rifampicin resistance with respect to smear status

We identified four studies that compared Xpert Ultra and Xpert MTB/RIF accuracy for rifampicin resistance detection by smear status (Figure 11) (Chakravorty 2017; Dorman 2018; Mishra 2020b; Piersimoni 2019).

Figure 11. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for the detection of rifampicin resistance by smear status. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



For smear-positive specimens, Xpert Ultra pooled sensitivity and specificity were 93.9% (84.4 to 97.7) and 99.3% (97.8 to 99.9) (4 studies, 686 participants) versus Xpert MTB/RIF pooled sensitivity and specificity of 95.5% (88.4 to 98.6) and 99.1% (97.3 to 99.9) (4 studies, 699 participants). The pooled specificity estimates for Xpert Ultra and Xpert MTB/RIF were similar. The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at −1.5% (−10.9 to 6.0) for sensitivity and 0.1% (−1.5 to 2.0) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.32. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 0.41 (Table 3).

For smear-negative specimens, Xpert Ultra pooled sensitivity and specificity were 92.0% (75.0 to 95.8) and 99.4% (96.2 to 100) (4 studies, 412 participants) versus Xpert MTB/RIF pooled sensitivity and specificity of 95.4% (82.3 to 99.3) and 99.2% (94.8 to 100) (4 studies, 416 participants). The pooled specificity estimates for Xpert Ultra and Xpert MTB/RIF were similar. The difference in the accuracy of Xpert Ultra minus Xpert MTB/RIF was estimated at −3.1% (−20.7 to 11.7) for sensitivity and 0.1% (−3.0 to 4.5) for specificity. We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF as 0.30. We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF as 0.42 (Table 3).

Indeterminate results, detection of rifampicin resistance

Regarding Xpert Ultra, four studies reported indeterminate results for rifampicin resistance: 21/76 (27.6%) Mishra 2020b; 14/80 (17.5%) Mishra 2020a; 16/684 (2.3%) Dorman 2018; 5/214 (2.3%) Wang 2019. Among four studies involving 1054 tests, the pooled proportion of indeterminate rifampicin resistance results for Xpert Ultra was 7.6% (2.4 to 21.0). Importantly, two studies reported the number of trace results that contributed to indeterminate rifampicin resistance results. In both studies, all or almost all indeterminate results were due to trace results, 13/14 (92.9%) in Mishra 2020a and 21/21 (100%) in Mishra 2020b.

Regarding Xpert MTB/RIF, three studies reported indeterminate results for rifampicin resistance: 1/61 (1.6%) Mishra 2020a; 1/67 (1.5%) Mishra 2020b; 4/684 (0.6%) Dorman 2018. Among three studies involving 812 tests, the pooled proportion of indeterminate test results for Xpert MTB/RIF was low, at 0.8% (0.2 to 2.4).

The estimated difference in the pooled proportion of indeterminate rifampicin resistance results for Xpert Ultra versus Xpert MTB/RIF was 6.7% (1.4 to 20.1). We estimated the probability that the pooled proportion of indeterminate results for Xpert Ultra exceeds that for Xpert MTB/RIF as 1.00.

Xpert Ultra trace results

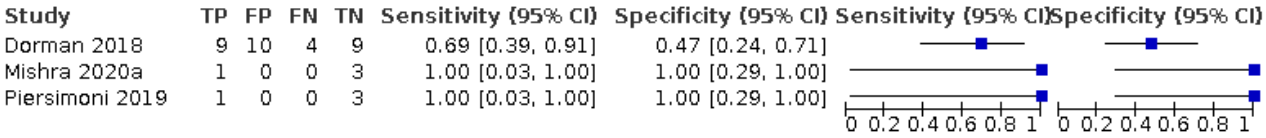
Summary of Xpert Ultra trace positive results

Eight studies reported the number of Xpert Ultra positive results that were trace-positives (Berhanu 2018; Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Pereira 2020; Piersimoni 2019; Wang 2019). The percentage of trace-positive results ranged from 3.0% to 30.4% (Table 5). Among participants with trace-positive results, four studies reported the percentage of participants with a history of tuberculosis: 20% (10.3% trace) in Berhanu 2018, 57.9% (7.1% trace) in Dorman 2018, 46.2% (18.6% trace) in Mishra 2020a, and 100% (27.6% trace) in Mishra 2020b. Mishra 2020b recruited participants with a recent history of tuberculosis (within the last two years) (Table 5).

Xpert Ultra repeated test for diagnosing pulmonary tuberculosis in people who have an initial Ultra trace result

We identified three studies where an Xpert Ultra repeated test was used to diagnose pulmonary tuberculosis in people who had an initial Ultra trace result, against culture: Mishra 2020a (4 participants), Piersimoni 2019 (4 participants), and Dorman 2018 (32 participants). Piersimoni 2019 retested the same initial samples. Dorman 2018 retested on a separately collected sputum sample. Mishra 2020a retested only those participants with discrepant (Ultra trace-positive/culture-negative) results, and retesting was performed on new specimens obtained a median of 444 days (range 245 to 526 days) after initial testing. Xpert Ultra accuracy of a second (repeat) test in Mishra 2020a and Piersimoni 2019 was 100% for both sensitivity and specificity. Dorman 2018 found sensitivity of 69% (95% CI 39 to 91) and specificity of 47% (24 to 71) (Table 5, Figure 12).

Figure 12. Forest plots of repeated Xpert Ultra sensitivity and specificity for detection of pulmonary tuberculosis in adults with initial trace result, culture reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative



Nontuberculous mycobacteria

Three studies reported the number of NTMs that grew from the specimens tested (total of 26 NTMs): Berhanu 2018 (4/244); Piersimoni 2019 (15/269); and Wang 2019 (7/498). Only one of these studies reported on Xpert Ultra and Xpert MTB/RIF results in those with NTM (Piersimoni 2019), and found neither test was positive in those who grew NTMs.

Sensitivity analyses

For Xpert Ultra for the detection of pulmonary tuberculosis, we undertook sensitivity analyses by limiting inclusion in the meta-analysis to the following.

- Studies where a single specimen yielded a single Xpert Ultra result for a given participant. We excluded studies that included more specimens than participants.
- Studies that only included untreated participants.
- Studies that used liquid culture as the reference standard.
- Studies where a consecutive or random sample of participants was enrolled.
- Studies where the reference standard was blinded.
- Studies that only used fresh specimens.

For Xpert Ultra for the detection of pulmonary tuberculosis, these sensitivity analyses made little difference to any of the findings (Table 6). We planned to perform a sensitivity analysis for studies that accounted for all participants in the analysis; however, for the detection of pulmonary tuberculosis, this criterion was satisfied by all studies.

DISCUSSION

This Cochrane Review on the diagnostic accuracy of Xpert Ultra compared to Xpert MTB/RIF for the detection of pulmonary tuberculosis and rifampicin resistance in adults summarizes the current literature. For the detection of pulmonary tuberculosis, we identified nine studies, of which seven were conducted in unselected participants. Estimation of accuracy in unselected patients is consistent with the intended use of these tests. For the detection of rifampicin resistance, we identified five studies.

Summary of main results

- For the detection of pulmonary tuberculosis, Xpert Ultra sensitivity and specificity were 90.9% (86.2 to 94.7) and 95.6% (93.0 to 97.4).
- For the detection of pulmonary tuberculosis, Xpert MTB/RIF sensitivity and specificity were 84.7% (78.6 to 89.9) and 98.4% (97.0 to 99.3).
- Xpert Ultra sensitivity and specificity were 77.5% (67.6 to 85.6) and 95.8% (92.9 to 97.7) for smear-negative, culture-positive tuberculosis.
- Xpert MTB/RIF sensitivity and specificity were 60.6% (48.4 to 71.7) and 98.8% (97.7 to 99.5) for smear-negative, culture-positive tuberculosis.
- Xpert Ultra sensitivity and specificity for pulmonary tuberculosis were 87.6% (75.4 to 94.1) and 92.8% (82.3 to 97.0) in people living with HIV.
- Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis were 74.9% (58.7 to 86.2) and 99.7% (98.6 to 100) in people living with HIV.

- Xpert Ultra sensitivity and specificity for pulmonary tuberculosis in people with a history of tuberculosis were 84.2% (72.5 to 91.7) and 88.2 (70.5 to 96.6).
- Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in people with a history of tuberculosis were 81.8% (68.7 to 90.0) and 97.4% (91.7 to 99.5).
- For the detection of pulmonary tuberculosis, the pooled proportion of Xpert Ultra non-determinate test results was low, 2.0% (0.9 to 3.6).
- For the detection of pulmonary tuberculosis, the pooled proportion of Xpert MTB/RIF non-determinate test results was low, 1.6% (0.8 to 3.0).
- For the detection of rifampicin resistance, Xpert Ultra sensitivity and specificity were 94.9% (88.9 to 97.9) and 99.1% (97.7 to 99.8).
- For the detection of rifampicin resistance, Xpert MTB/RIF sensitivity and specificity were 95.3% (90.0 to 98.1) and 98.8% (97.2 to 99.6).
- For the detection of rifampicin resistance, the pooled proportion of Xpert Ultra indeterminate test results was 7.6% (2.4 to 21.0).
- For the detection of rifampicin resistance, the pooled proportion of Xpert MTB/RIF indeterminate test results was 0.8% (0.2 to 2.4).

Detection of pulmonary tuberculosis

If the point estimates for Xpert Ultra and Xpert MTB/RIF are applied to a hypothetical cohort of 1000 people, where 10% of those presenting with symptoms have pulmonary tuberculosis, Xpert Ultra will miss 9 cases, and Xpert MTB/RIF will miss 15 cases. The number of people wrongly diagnosed with pulmonary tuberculosis would be 40 with Xpert Ultra and 14 with Xpert MTB/RIF (Summary of findings 1).

Detection of rifampicin resistance

If the point estimates for Xpert Ultra and Xpert MTB/RIF are applied to a hypothetical cohort of 1000 people, where 10% of those presenting with symptoms have rifampicin resistance, Xpert Ultra will miss 5 cases, and Xpert MTB/RIF will miss 5 cases. The number of people wrongly diagnosed with rifampicin resistance would be 8 with Xpert Ultra and 11 with Xpert MTB/RIF (Summary of findings 2).

Xpert Ultra performance in different subgroups

Xpert MTB/RIF detects DNA sequences of *M tuberculosis* after amplification, and has a lower limit of detection of 131 CFUs/mL (Helb 2010). The cycle threshold value (C_T) is the number of PCR cycles after which Xpert MTB/RIF probes successfully detect *M tuberculosis* DNA in a given sample. Xpert MTB/RIF C_T values are strongly correlated with acid-fast bacillus (AFB) smear status (Lange 2017). The lower sensitivity of Xpert MTB/RIF in individuals with AFB smear-negative pulmonary tuberculosis is related to the lower bacillary burden and higher associated C_T value compared to individuals with AFB smear-positive pulmonary tuberculosis. Individuals with pulmonary tuberculosis and HIV co-infection are more likely to have smear-negative tuberculosis, which implies a lower bacillary burden and higher mean C_T values on Xpert testing (Beynon 2018; Lange 2017); this is the likely mechanism for the lower sensitivity of Xpert Ultra for the diagnosis of tuberculosis in people living with HIV.

Xpert Ultra was developed to improve sensitivity in the detection of pulmonary tuberculosis, in particular in people with smear-negative disease and people living with HIV. In smear-negative, culture-positive pulmonary tuberculosis, we found Xpert Ultra sensitivity of 77.5% as compared to Xpert MTB/RIF sensitivity of 60.6%; in people living with HIV, Xpert Ultra sensitivity was 87.6% as compared to Xpert MTB/RIF sensitivity of 74.9%. The improvement in Xpert Ultra sensitivity came at the expense of a slight reduction in specificity as compared to Xpert MTB/RIF.

In individuals with a history of tuberculosis, we found that Xpert Ultra pooled specificity (88.2%) was considerably lower than the pooled specificity in the primary analysis (95.6%). Hence, the increase in sensitivity of Xpert Ultra as compared to Xpert MTB/RIF comes at the expense of specificity. Dorman and colleagues found that specificity improved as time since the previous diagnosis of tuberculosis increased, and approximated to that of participants without a history of tuberculosis when elapsed time was seven years (Dorman 2018). In comparison, for Xpert MTB/RIF in individuals with a history of tuberculosis, we found that Xpert MTB/RIF pooled specificity (97.4%) was only slightly lower than the pooled specificity in the primary analysis (98.4%). Other studies have reported that Xpert MTB/RIF may be positive at the end of tuberculosis treatment despite cure (Friedrich 2013; Theron 2016; Theron 2018), and may rarely remain positive for up to five years after tuberculosis treatment (Boyles 2014).

Regarding the prevalence of tuberculosis, in comparing settings with a higher or lower prevalence of tuberculosis, we previously reported that for both Xpert MTB/RIF sensitivity and specificity, the 95% CrIs in the two groups did not overlap, suggesting an association of prevalence of tuberculosis with the accuracy estimates (Horne 2019). In comparing settings with a higher or lower prevalence of rifampicin resistance, we also previously found that the CrIs for specificity did not overlap, suggesting an association of prevalence of rifampicin resistance with the specificity estimates (Horne 2019). Changes in disease prevalence have often been found to be associated with other important changes, such as in the disease spectrum, which may affect diagnostic accuracy estimates (Leeflang 2013). In this review, we did not analyse the effect of tuberculosis prevalence on Xpert Ultra accuracy. However, we acknowledge that as Xpert Ultra is rolled out globally, differences in accuracy may have important ramifications depending on the prevalence of tuberculosis and rifampicin resistance (Kendall 2017).

For the detection of rifampicin resistance, Xpert Ultra and Xpert MTB/RIF had similar sensitivity and specificity. Of interest, a recent prospective population-based study in Rwanda, a country with a low prevalence of rifampicin resistance, found that among patients with rifampicin resistance on initial Xpert MTB/RIF testing, 47% (57/121) had a false-positive rifampicin resistance result, in particular in specimens with a low tuberculosis bacillary burden (Ngabonziza 2020). As mentioned above, in order to address limitations in rifampicin resistance detection, Xpert Ultra uses melting temperature-based analysis, in lieu of real-time PCR analysis with Xpert MTB/RIF. Melting temperature-based analysis allows Xpert Ultra to better distinguish resistance-conferring mutations from silent mutations (Global Laboratory Initiative 2017).

To improve the sensitivity of Xpert Ultra, a new result category, trace call, was added, which corresponds to the lowest bacillary burden for *M tuberculosis* detection. The results of our systematic review suggest that Xpert Ultra trace calls are not a rare finding.

In the included studies, Xpert Ultra positive results that were trace-positives ranged from 7% to 30%. Of interest, Dorman 2018 performed several post hoc analyses that evaluated the impact of changing the classification of Xpert Ultra trace calls, which in the primary analysis were considered positive for the identification of *M tuberculosis*. Reclassifying all trace calls as a negative result increased Xpert Ultra specificity and decreased its sensitivity. When reclassifying trace calls as negative in participants with a history of tuberculosis, or repeating trace calls with the second result determining the ultimate classification, both resulted in sensitivity estimates close to those observed in the primary analysis, with only slightly compromised specificity.

We identified a higher number of rifampicin resistance indeterminate results with Xpert Ultra (7.6%) compared to Xpert MTB/RIF (0.8%). Notably, in studies that reported the number of trace results that contributed to indeterminate rifampicin resistance results, all, or almost all, Xpert Ultra indeterminate rifampicin resistance results were due to trace-positive results: 92.9% in Mishra 2020a and 100% in Mishra 2020b. The interpretation of and need for additional testing in patients with trace results will depend on clinical and epidemiological considerations.

We identified very limited data from patients who underwent repeated Ultra testing after an initial trace-positive result. With repeated testing against culture as the reference test, Dorman 2018 found Xpert Ultra sensitivity of 69% and specificity of 47% (32 participants), whereas Mishra 2020a (4 participants) and Piersimoni 2019 (4 participants) found Xpert Ultra sensitivity of 100% and specificity of 100%. Based on the findings in Dorman 2018, WHO recommended that "among persons without HIV infection with an initial trace call positive result, a fresh specimen from the patient should undergo repeat testing and the result of the second Ultra test be used for clinical decisions" (WHO 2017). The issue of how trace call results should be interpreted was recently reconsidered by the WHO with the following guidance: “For patients with Xpert Ultra trace results, decisions regarding treatment initiation should include considerations of the clinical presentation and the patient context (including prior treatment history, probability of relapse and other test results)" (WHO Consolidated Guidelines (Module 3) 2020).

We summarized data for NTM separately by determining the per cent of false-positive Xpert Ultra results in specimens that grew NTMs. We found that among specimens that were culture-positive for NTM, false-positive Xpert Ultra results did not occur. In an analytical study, Chakravorty assessed in triplicate the specificity of Xpert Ultra on 30 different NTMs for cross-reactivity, and found “MTB not detected” for all replicates tested (Chakravorty 2017).

We previously assessed whether Xpert MTB/RIF accuracy differs according to setting in which the test is performed, that is point of care or peripheral settings compared with central and intermediate laboratories (Horne 2019). Although we did not repeat this analysis for Xpert Ultra (both index tests are run identically), we consider it important to mention the findings from the previous review. When comparing results from studies by test setting, we found the pooled point estimates of Xpert MTB/RIF sensitivity and specificity to be lower in peripheral settings than in central and intermediate laboratories. However, there was considerable overlap in the credible intervals of these estimates, and evidence is insufficient to suggest a difference in Xpert MTB/RIF accuracy by setting. One of the confounding factors may be participant spectrum, the direction of which we cannot predict with certainty (Horne 2019). Of note, Theron and colleagues found no difference in Xpert MTB/RIF accuracy when performed by trained nurses in a primary care setting compared to performance by laboratory technicians at a centralized facility (Theron 2014b).

Patient-important outcomes are especially relevant to patients, decision-makers, and the wider tuberculosis community. We are not aware of direct evidence of the effect of Xpert Ultra on patient outcomes; however, two meta-analyses of the impact of Xpert MTB/RIF compared the effect of Xpert MTB/RIF and smear microscopy on all-cause mortality. Di Tanna and colleagues summarized the accuracy of Xpert MTB/RIF in an individual patient-level data meta-analysis (3 trials, 8143 participants) (Di Tanna 2019), and Haraka and colleagues performed a systematic review and meta-analysis (5 trials, 10,409 participants) (Haraka 2018; WHO Consolidated Guidelines (Module 3) 2020). In both analyses, Xpert MTB/RIF did not show a statistically significant effect on all-cause mortality, though the direction of effect was towards mortality reduction. These findings require careful interpretation, as the lack of statistical significance of impact of Xpert MTB/RIF on mortality may not indicate a lack of impact, but rather a lack of evidence of a difference (Altman 1995; Greenland 2016). Insufficient power to detect mortality in randomized trials measuring the impact of diagnostic tests on patient-important outcomes has been previously discussed as a limitation of such trials (Di Tanna 2019; Schumacher 2019). Early detection of tuberculosis and rifampicin resistance may not lead to improved patient outcomes if the test result is not linked to appropriate treatment and other healthcare services (Pai 2018).

In a systematic review of economic evaluations (28 studies), Zwerling and colleagues summarized costs, cost-effectiveness, and affordability of molecular tests for tuberculosis, including Xpert MTB/RIF, Xpert Ultra, and Truenat (Molbio Diagnostics, Goa, India). Most studies evaluated Xpert MTB/RIF; no studies evaluated Xpert Ultra; and one study evaluated Truenat (WHO Consolidated Guidelines (Module 3) 2020). Variations in costing, effectiveness, and epidemiological parameters were present in the included studies, making direct comparisons across studies challenging. The review found that the cost-effectiveness of Xpert MTB/RIF improved among populations with higher tuberculosis and HIV prevalence and in settings where rates of empirical tuberculosis treatment were low. Cost-effectiveness of Xpert MTB/RIF is dependent on a number of factors, including placement of GeneXpert machines (in centralized or decentralized facilities), testing volume, tuberculosis prevalence, level of empirical tuberculosis treatment, and pretreatment loss to follow-up (WHO Consolidated Guidelines (Module 3) 2020).

After the WHO recommended the use of Xpert MTB/RIF, country-level uptake was rapid. A 2018 survey of market penetration of Xpert MTB/RIF in high tuberculosis burden countries found greater use of Xpert MTB/RIF compared to smear microscopy for tuberculosis diagnosis (Cazabon 2018). There are currently no publications regarding market penetration of Xpert Ultra, which only requires new cartridges and a software update to existing GeneXpert machines. However, by the end of 2019, over 80 countries had procured Xpert Ultra tests. In more than 20 of these countries, Xpert Ultra conversion from MTB/RIF was greater than 90%. Examples of countries fully converted to Xpert Ultra are Eswatini

(high TB/HIV burden country); Lesotho (high tuberculosis burden and high TB/HIV burden country); Morocco; South Africa (high tuberculosis burden, high TB/HIV burden, high MDR-TB burden country); Uganda (high TB/HIV burden country); Ukraine (high MDR-TB burden country); and Zimbabwe (high tuberculosis burden, high TB/HIV burden, high MDR-TB burden country) (Denamps 2020 [pers comm]).

This review represents the most comprehensive review of the diagnostic accuracy of Xpert Ultra, including comparative accuracy studies of Xpert Ultra and Xpert MTB/RIF. Regarding Xpert MTB/RIF, previous reviews have provided additional findings (Horne 2019; Steingart 2014). These reviews provide evidence that may help countries make decisions about scaling up the tests for programmatic management of tuberculosis and drug-resistant tuberculosis. Although the information in this review will help inform such decisions, other factors such as resource requirements and feasibility (including stable electrical power supply, temperature control, and maintenance of the cartridge modules) will also be important considerations.

Application of the meta-analysis to a hypothetical cohort

Summary of findings 1 and Summary of findings 2 summarize the findings of our review by applying the results to a hypothetical cohort of 1000 individuals with presumptive pulmonary tuberculosis or rifampicin resistance. We have presented several different scenarios. For Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis, we used prevalences of tuberculosis of 2.5%, 10%, and 30%. For the detection of rifampicin resistance, we used prevalences of rifampicin resistance of 2%, 10%, and 15% (5% is estimated to be equivalent to the upper limit for rifampicin resistance prevalence in new cases; 15% is estimated to be the lower limit for rifampicin resistance prevalence among previously treated cases). The consequences of false-positive results are patient anxiety, morbidity from additional testing and unnecessary treatment, and possible delay in further diagnostic evaluation. The consequences of false-negative results are increased risk of patient morbidity and mortality, and continued risk of community transmission of tuberculosis.

Strengths and weaknesses of the review

Completeness of evidence

The findings in this review are based on comprehensive searching, strict inclusion criteria, and standardized data extraction. We had repeated correspondence with study authors to obtain additional data and missing information. The search strategy included studies published in all languages. Although we may have missed some studies despite the comprehensive search, we think it is unlikely that the findings would have changed. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) (McInnes 2018).

Accuracy of the reference standards used

Culture is regarded as the best available reference standard for active tuberculosis disease and was the reference standard for tuberculosis in this review (Lewinsohn 2017). We considered the type of culture used in the included studies because liquid culture is more sensitive than solid culture (American Thoracic Society 2000). Most studies did use liquid culture or a combination of solid and liquid culture; only one of the total nine studies exclusively used solid culture. For the culture reference standard, one study used only solid culture (Pereira 2020); five studies (56%) used only liquid culture (Dorman 2018; Mishra 2020a; Mishra 2020b; Opota 2019; Piersimoni 2019); and three studies (33%) used both solid and liquid cultures (Berhanu 2018; Chakravorty 2017; Wang 2019).

Phenotypic culture-based DST methods using WHO-recommended critical concentrations and line probe assays, WHO-recommended tests (WHO Consolidated Guidelines (Module 3) 2020), were the reference standards for rifampicin resistance. Regarding phenotypic culture-based DST, following completion of this review, the WHO published recommendations lowering critical concentrations for rifampicin resistance testing (MGIT and 7H10) to reduce misclassification of false resistance (WHO 2021). We will incorporate the new recommendations in future updates of this review. In this review, two of the total five studies used line probe assays (i.e. MTBDR*plus*) alone as the reference standard.

We assessed the number of specimens with NTMs that were Xpert Ultra- and Xpert MTB/RIF-positive. Three studies reported a total of 26 NTMs that grew from the specimens tested. Only one of these studies reported on Xpert Ultra and Xpert MTB/RIF results in those with NTM (Piersimoni 2019), and found neither test was positive in those that grew NTMs. In the previous review, among 10 studies that reported information comprising 141 NTM, Xpert MTB/RIF was negative in all specimens (Horne 2019). Similarly, a study that assessed Xpert Ultra specificity using 20 culture-positive NTM specimens (covering a total of 18 species) found that Xpert Ultra was negative for all specimens (Perez-Risco 2018).

Quality of the included studies

Most studies used consecutive selection of participants and interpreted the reference standard results without knowledge of index test results. Xpert Ultra and MTB/RIF results are generated automatically, without requiring subjective interpretation. For pulmonary tuberculosis detection, using QUADAS-C, for patient selection, six studies had low risk of bias. We considered three studies to have high risk of bias: one study did not report the manner of participant selection (Chakravorty 2017); one study exclusively enrolled participants who had recently received tuberculosis treatment (Mishra 2020b); and one study exclusively enrolled smear-negative participants (Wang 2019). In general, studies were fairly well reported, although we corresponded with authors for additional data and missing information. We encourage the authors of future studies to follow the recommendations in the STARD (Standards for Reporting of Diagnostic Accuracy) statement to improve the quality of reporting (Bossuyt 2015).

Interpretability of subgroup analyses

We investigated potential sources of heterogeneity in different subgroups. For tuberculosis detection, Xpert Ultra had higher sensitivity in smear-positive and HIV-negative participants. Importantly, we found Xpert Ultra to have higher sensitivity and lower specificity than Xpert MTB/RIF in smear-negative participants and people living with HIV, two subgroups in which Xpert MTB/RIF has suboptimal sensitivity. In individuals with a history of tuberculosis, we found that Xpert Ultra pooled specificity was considerably lower than the pooled specificity in the primary analysis. Hence, the increase in sensitivity of Xpert Ultra as compared to Xpert MTB/RIF comes at the expense of specificity.

As there were small numbers of studies in these analyses, results should be interpreted with caution.

Comparison with other systematic reviews

We are aware of one previously published systematic review that estimated the diagnostic accuracy of Xpert Ultra for pulmonary tuberculosis and rifampicin resistance in adults (Zhang 2019). For the detection of pulmonary tuberculosis, this review found pooled sensitivity of 88.5% (95% CI 82.1 to 92.9) and specificity of 96.7% (95% CI 95.1 to 97.8), similar to the findings of our review (pooled sensitivity 90.9%, 95% CrI 86.2 to 94.7 and pooled specificity 95.6%, 95% CrI 93.0 to 97.4). For the detection of rifampicin resistance, Xpert Ultra accuracy estimates were also similar to those in our review. Another study included adults and children and assessed Xpert Ultra and Xpert MTB/RIF performance in both pulmonary and extrapulmonary tuberculosis (Jiang 2020). We identified several systematic reviews on the diagnostic accuracy of Xpert MTB/RIF, which are summarized in Table 7.

Compared with previous systematic reviews, our review had a more recent search date thus increasing the number of potential studies for inclusion. Our strict inclusion criteria, for example including only studies that used culture as the reference standard and excluding case-control studies, meant that some studies included in other reviews were excluded from our review.

Completeness and relevance of the review

Our review included studies using all four previous generations of Xpert MTB/RIF (G1, G2, G3, G4 cartridges) and the newest version, Xpert Ultra. We have included studies that compared the accuracy of Xpert Ultra and Xpert MTB/RIF for diagnosing pulmonary tuberculosis and rifampicin resistance. Our review, plus information previously reported in Horne 2019, present a reasonably complete assessment of the accuracy of these tests. A Cochrane Review on Xpert MTB/RIF for extrapulmonary tuberculosis (including 11 studies evaluating Xpert Ultra) was published (Kohli 2021). This review found that in people with presumptive extrapulmonary tuberculosis, Xpert Ultra and Xpert MTB/RIF may be helpful in confirming the diagnosis. Test sensitivity varied across different extrapulmonary specimens, while for most specimens specificity was high. In addition, Xpert Ultra and Xpert MTB/RIF had similar accuracy for the detection of rifampicin resistance (Kohli 2021). A Cochrane Review update on Xpert MTB/RIF and Xpert Ultra for extrapulmonary tuberculosis is under way. A Cochrane Review on Xpert MTB/RIF and Xpert Ultra for active tuberculosis (pulmonary and extrapulmonary) in children was recently published (Kay 2020).

Applicability of findings to the review question

For the detection of pulmonary tuberculosis, we had low concern for most studies in the index test and reference standard domains. In the patient selection domain, we considered only four studies (44%) to have low concern because participants in these studies were evaluated in primary care facilities, local hospitals, or both settings consistent with the intended use of the test. For the detection of rifampicin resistance, we also had low concern for all QUADAS-2 domains except for patient selection, where we considered only one of five studies to have low concern for applicability.

AUTHORS' CONCLUSIONS

Implications for practice

For diagnosing pulmonary tuberculosis, we found Xpert Ultra to have higher sensitivity and lower specificity than Xpert MTB/RIF, especially in smear-negative participants and people living with HIV. Xpert Ultra specificity was lower than that of Xpert MTB/RIF in participants with a history of tuberculosis. The sensitivity and specificity trade-off would be expected to vary by setting. For the detection of rifampicin resistance, Xpert Ultra and Xpert MTB/RIF had similar sensitivity and specificity. Ultra trace-positive results were common. For patients with Xpert Ultra trace-positive results, decisions regarding treatment initiation should include considerations of the clinical presentation and the patient context (including prior treatment history, probability of relapse, and other test results). Xpert Ultra and Xpert MTB/RIF provide accurate results and can allow rapid initiation of treatment for rifampicin-resistant and multidrug-resistant tuberculosis.

Implications for research

Future studies should assess the diagnostic accuracy of Xpert Ultra compared with other rapid tests for tuberculosis and drug resistance, especially in difficult-to-diagnose groups, that is children, people living with HIV, and those with extrapulmonary tuberculosis. Understanding the impact of Xpert Ultra in settings with differing prevalence of tuberculosis, in people with a history of tuberculosis, with varying strategies for the classification of trace calls, and its impact on people-important outcomes will be important. The ongoing use of Xpert Ultra or Xpert MTB/RIF in tuberculosis programmes in high tuberculosis burden settings, as well as their use in primary care clinics, where the test provides the opportunity to begin treatment promptly, will contribute evidence on whether their use leads to improvements in patient health. There is an urgent need for studies that investigate strategies for responding to Ultra trace-positive results. Operational research is needed to ensure that tests are optimally used in settings of intended use.

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CHARACTERISTICS OF STUDIES

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

Berhanu 2018

Study characteristics	
Patient Sampling	Cohort, all participants received Xpert MTB/RIF, and the order by which participants were selected to receive Xpert Ultra was randomized, prospective
Patient characteristics and setting	Presenting signs and symptoms: adults (18 years old) who presented with at least 1 TB symptom, which included cough of any duration, fever, weight loss, and night sweats Age: median 36 years (range 18 to 77) Sex, female: 33% HIV infection: 62% History of TB: 18% Sample size: 237 Clinical setting: outpatient Laboratory level: central 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: 27%

Berhanu 2018 *(Continued)*

Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis LJ and MGIT; composite based on clinical and radiological findings Rifampicin resistance LJ, MGIT, MTBDR*plus* 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)			
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		

Berhanu 2018 *(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 for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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	

Chakravorty 2017

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, retrospective for FIND biobank specimens, prospective for clinical specimens; paired design, Xpert Ultra was tested retrospectively on a frozen aliquot of the fresh sputum specimen originally tested with Xpert MTB/RIF
Patient characteristics and setting	Presenting signs and symptoms: participants presenting with symptoms compatible with TB Age: adult Sex, female: not reported HIV infection: not reported History of TB: not reported Sample size: 277

Chakravorty 2017 *(Continued)*

	Clinical setting: not reported Laboratory level: central Country: FIND biobank frozen specimens (Peru, Vietnam, South Africa) and clinical specimens (Georgia, India) World Bank Income Classification: middle and low High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study: 72%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis LJ and MGIT (data provided based on MGIT) Rifampicin resistance LJ and MGIT Speciation: yes
Flow and timing	
Comparative	
Notes	212 frozen specimens were included from FIND biobank. Ultra was tested retrospectively on a frozen aliquot of the same sputum sample tested with Xpert MTB/RIF (fresh sample).

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear 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		

Chakravorty 2017 *(Continued)*

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)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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	

Dorman 2018

Study characteristics	
Patient Sampling	Cohort, consecutive enrolment, prospective data collection, multicentre study, paired design with Xpert

Dorman 2018 *(Continued)*

	Ultra and Xpert MTB/RIF tested on the same sputum sample
Patient characteristics and setting	Presenting signs and symptoms: presumed pulmonary TB Age: adults, median 28 years (IQR 28 to 50) Sex, female: 40% HIV infection: 44% History of TB: 21% Sample size: 1439 for detection of *Mycobacterium tuberculosis*, 551 for rifampicin resistance Clinical setting: both outpatient and inpatient Laboratory level: central (reference) Country: Belarus, Brazil, China, Georgia, India, Kenya, South Africa, Uganda World Bank Income Classification: low and middle income High TB burden country: yes (Brazil, China, India, Kenya, South Africa) High MDR-TB burden country: yes (Belarus, China, India, Kenya, South Africa) High TB/HIV burden country: yes (Brazil, China, India, Kenya, South Africa, Uganda) Prevalence of TB cases in the study: 32%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis LJ and MGIT Rifampicin resistance MGIT Speciation: yes
Flow and timing	
Comparative	
Notes	25 participants (3%) who were smear-positive but in whom all cultures were negative were excluded from the analysis.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Dorman 2018 *(Continued)*

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)			
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?	Unclear		
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 for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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			

Dorman 2018 *(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?	No
Could the patient flow have introduced bias?	Low risk

Mishra 2020a

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective. Paired design; collected 3 sputum samples from each patient, 2 at the first visit, of which 1 was tested using Xpert and the other was tested using culture, and 1 sample the next morning, which was tested using Ultra
Patient characteristics and setting	Presenting signs and symptoms: presumptive pulmonary TB according to the WHO Age: ≥ 18 years; median 37 years (IQR 27 to 50) Sex, female: 49% HIV infection: 20% History of TB: 39% Sample size: 239 Clinical setting: outpatient Laboratory level: central 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: 30%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT Rifampicin resistance MTBDR*plus* Speciation: yes

Mishra 2020a *(Continued)*

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)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		

Mishra 2020a *(Continued)*

Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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

Mishra 2020b

Study characteristics	
Patient Sampling	Cross-sectional, random selection (1:1 testing Xpert Ultra or Xpert MTB/RIF), prospective
Patient characteristics and setting	Presenting signs and symptoms: preselected for recent (< 2 years) previous TB treatment Age: ≥ 18 years; median 37.5 (30 to 50) Sex, female: 40% HIV infection: 44% History of TB: 100% Sample size: 346 Clinical setting: unknown Laboratory level: central 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: 26%
Index tests	Xpert MTB/RIF OR Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis

Mishra 2020b *(Continued)*

	MGIT Rifampicin resistance MTBDR*plus* Speciation: yes
Flow and timing	Of 124 participants tested with Xpert Ultra, 18 were rifampicin resistant indeterminate; of 127 participants tested with Xpert MTB/RIF, only 1 participant was rifampicin resistant indeterminate.
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?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			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)			
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	

Mishra 2020b *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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	

Opota 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective and retrospective; Xpert MTB/RIF assay was tested on some fresh and some frozen specimens, whereas Xpert Ultra was performed only on frozen specimens paired with Xpert MTB/RIF
Patient characteristics and setting	Presenting signs and symptoms: suspected pulmonary tuberculosis Age: unknown Sex, female: not reported HIV infection: not reported History of TB: not reported Sample size: 196 Clinical setting: laboratory-based evaluation in a hospital using the index test for decisions regarding the need for airborne isolation

Opota 2019 *(Continued)*

	Laboratory level: central Country: Switzerland World Bank Income Classification: high High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: no Prevalence of TB cases in the study: 24%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite based on clinical, X-ray, and other methods Rifampicin resistance MGIT Speciation: not reported
Flow and timing	
Comparative	
Notes	Study included 69 frozen specimens. When considering the 47 culture-positive specimens, all of the isolates were phenotypically susceptible to rifampicin.

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		

Opota 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)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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?			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	

Pereira 2020

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective; paired design, all samples were tested with Xpert Ultra and Xpert MTB/RIF

Pereira 2020 *(Continued)*

Patient characteristics and setting	Presenting signs and symptoms: respiratory symptoms suggestive of pulmonary tuberculosis, such as productive cough for > 2 weeks, cough of any duration accompanied by constitutional symptoms (fever for at least 3 days, night sweats or weight loss of at least 3 kg in the previous month), or haemoptysis Age: > 18 years; mean 50 years (SD 18) Sex, female: 44% HIV infection: 2% History of TB: 0% Sample size: 180 Clinical setting: outpatient Laboratory level: intermediate Country: Brazil 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: 13%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis Ogawa-Kudoh method 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	

Pereira 2020 *(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)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Unclear		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?			
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	

Piersimoni 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, retrospective, frozen specimens; paired design, Xpert Ultra was tested on a frozen aliquot of the fresh sputum specimen originally tested with Xpert MTB/RIF
Patient characteristics and setting	Presenting signs and symptoms: patients presenting with tuberculosis symptoms and abnormal X-ray imaging Age: median 42 years (range 7 to 91, with only 2/254 participants below 15 years) Sex, female: 37% HIV infection: not reported History of TB: excluded from study Sample size: 266 Clinical setting: tertiary hospital (majority were inpatients, < 10% outpatients) Laboratory level: central Country: Italy World Bank Income Classification: high High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: no Prevalence of TB cases in the study: 46%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT Rifampicin resistance MGIT Speciation: yes
Flow and timing	
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Piersimoni 2019 *(Continued)*

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)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	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			

Piersimoni 2019 *(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

Wang 2019

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective; paired design, Xpert Ultra assay was tested on frozen specimens and Xpert MTB/RIF on fresh specimens
Patient characteristics and setting	Presenting signs and symptoms: patients with tuberculosis symptoms suspected of having pulmonary tuberculosis, smear-negative Age: median 47 years (range 14 to 89), smear-negative pulmonary tuberculosis Sex, female: 34% HIV infection: 0% History of TB: 50% Sample size: 498 Clinical setting: national-level tuberculosis referral centre, inpatients Laboratory level: central Country: China 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: 24%
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	Pulmonary tuberculosis LJ and MGIT Rifampicin resistance LJ Speciation: yes

Wang 2019 *(Continued)*

Flow and timing	
Comparative	
Notes	Xpert Ultra was tested using specimens stored at −80 °C.

Methodological quality

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

Wang 2019 *(Continued)*

Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Unclear	
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?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Abbreviations: ICU: intensive care unit; IQR: interquartile range; LJ: Löwenstein–Jensen; MDR-TB: multidrug-resistant TB; MGIT: Mycobacteria Growth Indicator Tube; MODS: microscopic observation drug susceptibility; SD: standard deviation; TB: tuberculosis; WHO: World Health Organization

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

Study	Reason for exclusion
Abong 2019	Xpert Ultra not evaluated
Acuna-Villaorduna 2017	Duplicate data with additional analyses; Boum 2016 includes same data set
Ade 2016	Includes both adults and children, or no information about age of enrolment
Adelman 2014	Abstract
Afshan 2019	Xpert Ultra not evaluated
Agizew 2017	Data insufficient for 2 x 2 table
Agizew 2019	Xpert Ultra not evaluated
Agrawal 2016	Includes both adults and children, or no information about age of enrolment
Agustina 2019	Paediatric population
Ai 2019	Xpert Ultra not evaluated
Akhter 2019	Xpert Ultra not evaluated
Alame-Emane 2017	Data insufficient for 2 x 2 table
Al-Ateah 2012	Includes both adults and children, or no information about age of enrolment
Albay 2016	Includes both adults and children, or no information about age of enrolment

Study	Reason for exclusion
Al-Darraji 2016	Data insufficient for 2 x 2 table
Allahyartorkaman 2019	Xpert Ultra not evaluated
Alland 2015	Abstract
Alnimr 2014	Data insufficient for 2 x 2 table
Alvarez 2015	Includes both adults and children, or no information about age
Alvarez-Uria 2012	Reference standard not satisfied
Alvis-Zakzuk 2017	Systematic review
Andriani 2016	Abstract
Antonenka 2013	Case-control study
Ardizzoni 2019	Xpert Ultra not evaluated
Aricha 2019	Xpert Ultra not evaluated
Armand 2011	This was a case-control study that compared Xpert MTB/RIF with an in-house IS6110-based real-time PCR using TaqMan probes (IS6110-TaqMan assay) for TB detection.
Asencio 2013	Cost-effectiveness study
Aston 2016	Abstract
Atashi 2017	Data insufficient for 2 x 2 table
Atehortua 2015	Includes both adults and children, or no information about age of enrolment
Atuhumuza 2016	Abstract
Atwine 2015	Data insufficient for 2 x 2 table
Auld 2016	Includes both adults and children
Aurin 2014	Includes both adults and children, or no information about age of enrolment
Avashia 2016	Reference standard not satisfied
Ayala 2016	Data insufficient for 2 x 2 table
Aydemir 2019	Xpert Ultra not evaluated
Bablishvili 2015	Includes both adults and children, or no information about age of enrolment
Badal-Faesen 2017	Duplicate data with additional analyses; Luetkemeyer 2016 includes same data set
Baikunje 2019	Xpert Ultra not evaluated
Bajrami 2016	Includes data for pulmonary and extrapulmonary TB combined

Study	Reason for exclusion
Balcha 2014	Xpert was not the index test.
Banu 2014	Data insufficient for 2 x 2 table
Barcellini 2019	Community-based screening
Barkham 2016	Abstract
Barnard 2012	Includes both adults and children, or no information about age of enrolment
Bates 2013	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children.
Benjamin 2019	Xpert Ultra not evaluated
Bhardwaj 2019	Xpert Ultra not evaluated
Biadglegne 2014	Includes both adults and children, or no information about age of enrolment
Bilgin 2016	Includes both adults and children, or no information about age of enrolment
Bimba 2019	Xpert Ultra not evaluated
Bisognin 2018	Not a diagnostic accuracy study
Bjerrum 2015	Xpert was not the index test.
Boakye-Appiah 2016	Data insufficient for 2 x 2 table
Bojang 2016	Xpert was not the index test.
Bonnet 2017	Data insufficient for 2 x 2 table
Borodulina 2019	Xpert Ultra not evaluated
Boum 2016	Xpert Ultra not evaluated
Bowles 2011	Includes both adults and children, or no information about age of enrolment
Bunsow 2014	Includes respiratory specimens and gastric aspirates
Byashalira 2019	Xpert Ultra not evaluated
Capocci 2016	Abstract
Causse 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Cavanaugh 2016	Data insufficient for 2 x 2 table
Cayci 2017	Includes both adults and children, or no information about age of enrolment
Celik 2015	Includes both adults and children, or no information about age of enrolment
Chakraborty 2019	Xpert Ultra not evaluated
Chhajed 2019	Xpert Ultra not evaluated

Study	Reason for exclusion
Chishty 2016	Abstract
Ciftçi 2011	Includes both adults and children, or no information about age of enrolment
Clouse 2012	Study on patient impact
Cross 2014	Reference standard not satisfied
Cross 2015	Includes both adults and children, or no information about age of enrolment
Dagnra 2015	Data insufficient for 2 x 2 table
Dahale 2019	Xpert Ultra not evaluated
Daum 2015	Xpert not the index test
Deggim 2013	Includes both adults and children, or no information about age of enrolment
Dierberg 2016	Data insufficient for 2 x 2 table
Dorjee 2012	Case report
Dorman 2012	Prevalence survey
Dowdy 2011	Cost-effectiveness study
Eldin 2019	Xpert Ultra not evaluated
Elzein 2019	Xpert Ultra not evaluated
Fantahun 2019	Xpert Ultra not evaluated
Feasey 2013	Data insufficient for 2 x 2 table
Fernandez 2017	Abstract
FIND 2011	This study compared Xpert MTB/RIF G3 and G4. We excluded it owing to concerns about duplicate data. In addition, the criteria for the reference standard for rifampicin resistance detection were not satisfied.
Fong 2017	Abstract
Friedrich 2011	This study evaluated Xpert MTB/RIF for the diagnosis of pleural TB.
Gama de Andrade 2017	Abstract
Garcia-Basteiro 2019	Inappropriate reference standard
Gati 2018	Xpert Ultra not evaluated
Gelalcha 2017	Includes both adults and children, or no information about age of enrolment
Gounder 2014	Includes both adults and children, or no information about age of enrolment
Griesel 2016	Abstract

Study	Reason for exclusion
Griesel 2017	Includes data for pulmonary and extrapulmonary TB combined
Guenaoui 2016	Includes both adults and children, or no information about age of enrolment
Gupta 2014	Abstract
Gurbanova 2016	Abstract
Gurbanova 2017	Includes data for pulmonary and extrapulmonary TB combined
Gursoy 2016	Includes both adults and children, or no information about age of enrolment
Habeenzu 2017	Includes both adults and children, or no information about age of enrolment
Hai 2019	Xpert Ultra not evaluated
Hanifa 2016	Reference standard not satisfied
Heidebrecht 2016	Data insufficient for 2 x 2 table
Hillemann 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Hiza 2017	Not a diagnostic accuracy study
Ho 2016	Community-based screening
Hodille 2019	Only culture-positive specimens were tested; Xpert MTB/RIF was not evaluated.
Horo 2017	Includes both adults and children, or no information about age of enrolment
Hu 2014	Includes both adults and children, or no information about age of enrolment
Huang 2018	Includes both adults and children, or no information about age of enrolment
Huerga 2017	Xpert was not the index test.
Ioannidis 2010	We could not obtain this article.
Ioannidis 2011	Includes both adults and children, or no information about age of enrolment
Iram 2015	Includes both adults and children, or no information about age of enrolment
Jafari 2013	Data insufficient for 2 x 2 table
Jin 2019	Xpert Ultra not evaluated
Jing 2017	Includes both adults and children, or no information about age of enrolment
Jipa 2016	Abstract
Jones-Lopez 2014	Xpert was not the index test.
Kang 2016	Abstract
Kaur 2016	Systematic review

Study	Reason for exclusion
Kayigire 2013	Not a diagnostic accuracy study
Kazemian 2019	Xpert Ultra not evaluated
Kelly-Cirino 2017	Xpert was not the index test.
Kendall 2019	Case-control study
Kerkhoff 2013	Data insufficient for 2 x 2 table
Kerkhoff 2014	Data insufficient for 2 x 2 table
Khadka 2019	Xpert Ultra not evaluated
Khalil 2015	Includes both adults and children, or no information about age of enrolment
Khan 2016	Data insufficient for 2 x 2 table
Kim 2012	Case-control study
Kim CH 2014	Duplicate data; Kim CH 2015 includes the same data with more participants
Kim CH 2015	Xpert Ultra not evaluated
Kim MJ 2015	Data insufficient for 2 x 2 table
Kim YW 2015	Includes both adults and children, or no information about age of enrolment
Kolia-Diafouka 2019	Case-control study
Lange 2017	Systematic review
Laskar 2017	Could not obtain full text
Lawn 2012a	Study on patient impact
Lawn 2012b	Data insufficient for 2 x 2 table
Lawn 2012c	Primarily a lipoarabinomannan detection study
Lawn 2013	Data insufficient for 2 x 2 table
Lawn 2015	Reference standard not satisfied
Lawn 2017	Reference standard not satisfied
Lebina 2016	Community-based screening
Lessells 2017	Impact study
Li 2016	Includes both adults and children, or no information about age of enrolment
Li 2017	Systematic review
Li 2020	Xpert Ultra not evaluated

Study	Reason for exclusion
Ligthelm 2011	This study evaluated Xpert MTB/RIF for the diagnosis of TB lymphadenitis.
Lombardi 2017	Includes both adults and children, or no information about age of enrolment
Luetkemeyer 2016	Xpert Ultra not evaluated
Mafort 2017	Abstract
Malbruny 2011	Includes both adults and children, or no information about age of enrolment
Marlowe 2011	Includes both adults and children, or no information about age of enrolment
Matabane 2015	Includes both adults and children, or no information about age of enrolment
Mave 2017	Screening
Maynard-Smith 2014	Systematic review
Mechal 2019	Xpert Ultra not evaluated
Miller 2011	Includes both adults and children, or no information about age of enrolment
Miotto 2012	Treatment monitoring
Mntonintshi 2017	Data insufficient for 2 x 2 table
Modi 2016	Xpert was not the index test.
Mokaddas 2016	Abstract
More 2017	Data insufficient for 2 x 2 table
Morozova 2016	Abstract
Moure 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Mukherjee 2017	Reference standard not satisfied
Mulder 2017	Xpert was not the index test.
Muñoz 2013	Study on patient impact
Myneedu 2014	Includes both adults and children, or no information about age of enrolment
Naidoo 2016	Data insufficient for 2 x 2 table
Narasimooloo 2012	Study on patient impact
Ng 2018	Case-control study
Nguyen 2018	Includes both adults and children, or no information about age of enrolment
Ngwira 2017	Abstract
Nhu 2013	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children.

Study	Reason for exclusion
Nicol 2011	This study evaluated Xpert for the diagnosis of TB in children.
Ninan 2016	Xpert was not the index test.
Nosova 2013a	Duplicate data; same study as Nosova 2013b. Nosova 2013a is written in Russian.
Nosova 2013b	Xpert Ultra not evaluated
Ntinginya 2012	Active case finding, not a diagnostic test accuracy study
O'Grady 2012	This study evaluated Xpert MTB/RIF in patients able to produce sputum, irrespective of admission diagnosis, not presumed TB patients.
Oliveira 2019	Xpert Ultra not evaluated
Omar 2019	Xpert Ultra not evaluated
Omrani 2014	Not a diagnostic accuracy study
Opota 2016	Includes both adults and children, or no information about age of enrolment
Osman 2014	Case-control study
Ou 2015	Includes both adults and children, or no information about age of enrolment
Ozkutuk 2014	Includes both adults and children, or no information about age of enrolment
Pandey P 2017	Includes both adults and children, or no information about age of enrolment
Pandey S 2017	Includes both adults and children, or no information about age of enrolment
Parcell 2017	Includes both adults and children, or no information about age of enrolment
Patel 2020	Xpert Ultra not evaluated
Patil 2014	Case report
Patil 2017	Reference standard not satisfied
Peter 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Peter 2013	Data insufficient for 2 x 2 table
Peter 2015	Duplicate data; study was nested in Theron 2014b
Qureshi 2019	Xpert Ultra not evaluated
Rachow 2012	This study evaluated Xpert for the diagnosis of TB in children.
Rahman 2016	Not a diagnostic accuracy study
Raizada 2015	Not a diagnostic accuracy study
Ramamurthy 2016	Data insufficient for 2 x 2 table

Study	Reason for exclusion
Ramirez 2014	Not a diagnostic accuracy study
Rasheed 2019	Xpert Ultra not evaluated
Rathish 2019	Xpert Ultra not evaluated
Rathour 2019	Xpert Ultra not evaluated
Reechaipichitkul 2016	Duplicate data; more participants were included in Reechaipichitkul 2017
Reechaipichitkul 2017	Xpert Ultra not evaluated
Reed 2016	Xpert was not the index test.
Rees 2018	Impact study
Reis 2019	Xpert Ultra not evaluated
Rivera 2019	Xpert Ultra not evaluated
Rossato 2018	Study design unclear, possibly case-control
Rufai 2014	Data insufficient for 2 x 2 table
Ruiz 2017	Xpert was not the index test.
Sachdeva 2015	Not a diagnostic accuracy study
Saeed 2017	Data insufficient for 2 x 2 table
Sanchez-Padilla 2015	Not a diagnostic accuracy study
Sauzullo 2016	Includes both adults and children, or no information about age of enrolment
Schutz 2019	Xpert Ultra not evaluated
Set 2019	Xpert Ultra not evaluated
Shah 2014	Case-control study
Shah 2020	Xpert Ultra not evaluated
Sharma 2019	Did not include specimen of choice
Shenai 2013	Data insufficient for 2 x 2 table
Shenoy 2019	Xpert Ultra not evaluated
Shilpa 2017	Reference standard not satisfied
Simone 2019	Xpert Ultra not evaluated
Singh 2019	Xpert Ultra not evaluated
Smith 2014	Not a diagnostic accuracy study

Study	Reason for exclusion
Somashekar 2014	Reference standard not satisfied
Somily 2016	Includes both pulmonary and extrapulmonary specimens combined
Strydom 2015	Case-control study
Sumalani 2019	Xpert Ultra not evaluated
Sumayya 2019	Xpert Ultra not evaluated
Sun 2019	Paediatric population
Sureshbabu 2016	Reference standard not satisfied
Tadesse 2016	Abstract
Tahseen 2016	Drug resistance survey
Tahseen 2019	Xpert Ultra not evaluated
Talib 2019	Xpert Ultra not evaluated
Tan 2017	Xpert was not the index test.
Taylor 2012	This study evaluated Xpert for the diagnosis of extrapulmonary TB.
Teo 2011	Includes both adults and children, or no information about age of enrolment
Theron 2012	Treatment monitoring
Theron 2014a	Duplicate data set for Theron 2014a with a different aim
Theron 2016	Duplicate data. Author reported that this study overlaps with Theron 2014a and can be excluded.
Theron 2018	Screening study
Thibbadee 2016	Abstract
Thit 2017	Xpert was not the index test.
To 2017	Abstract
Tortoli 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Uddin 2019	Xpert Ultra not evaluated
Udgirkar 2019	Xpert Ultra not evaluated
Ullah 2016	Includes both adults and children, or no information about age of enrolment
Ullah 2017	Includes both adults and children, or no information about age of enrolment
Vadwai 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Van Kampen 2015	Includes both adults and children, or no information about age of enrolment

Study	Reason for exclusion
Van Rie 2011	Case report
Walters 2012	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children.
Walusimbi 2013	Systematic review
Wang 2015	Systematic review
Wang 2016	Includes both adults and children, or no information about age of enrolment
Williamson 2012	Case-control study
Wood 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB.
Xie 2017	Xpert was not the index test.
Yadav 2017	Includes both adults and children, or no information about age of enrolment
Yan 2016	Systematic review
Yang X 2020	Xpert Ultra not evaluated
Yeong 2019	Xpert Ultra not evaluated
Yu 2020	Xpert Ultra not evaluated
Zar 2012	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children.
Zar 2019	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children.
Zemlyansky 2016	Includes both adults and children, or no information about age of enrolment
Zhou 2020	Xpert Ultra not evaluated
Zimba 2019	Xpert Ultra not evaluated
Zurcher 2019	Xpert Ultra not evaluated

PCR: polymerase chain reaction; TB: tuberculosis

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

ChiCTR180001479

Study name	Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous bronchoalveolar lavage fluid in HIV-infected adults: a prospective cohort study
Target condition and reference standard(s)	Tuberculosis, HIV/AIDS
Index and comparator tests	Index test is Xpert MTB/RIF Ultra on bronchoalveolar lavage fluid in HIV-positive patients. Comparator tests will include Xpert MTB/RIF and culture.
Starting date	5 February 2018

ChiCTR180001479 *(Continued)*

Contact information	Yang Zhou; 516472422@qq.com
Notes	Chictr.org.cn Identifier: ChiCTR1800014792

ChiCTR1800014792

Study name	Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous bronchoalveolar lavage fluid in HIV-infected adults: a prospective cohort study
Target condition and reference standard(s)	Tuberculosis and HIV/AIDS, MGIT (Mycobacteria Growth Indicator Tube)
Index and comparator tests	Xpert Ultra
Starting date	12 February 2018
Contact information	Peize Zhang; 516472422@qq.com
Notes	WHO ICTRP: ChiCTR1800014792

ChiCTR1900026491

Study name	The diagnostic value of medical thoracoscopy combined with Xpert MTB/RIF Ultra in smear and culture negative pulmonary tuberculosis
Target condition and reference standard(s)	Tuberculosis (smear and culture negative)
Index and comparator tests	Index tests are Xpert MTB/RIF Ultra and thoracoscopy with comparator of pathologic diagnosis in smear and culture-negative pulmonary tuberculosis.
Starting date	12 October 2019
Contact information	Hairong Huang; huanghairong@tb123.org
Notes	Chictr.org.cn Identifier: ChiCTR1900026491

ISRCTN77241966

Study name	Evaluation of GeneXpert Ultra and digital chest radiography for diagnosing tuberculosis
Target condition and reference standard(s)	Tuberculosis, HIV/AIDS
Index and comparator tests	Index test is Xpert Ultra with comparator of Xpert or microscopy (current standard of care), with reference standard of bacteriologically confirmed TB.
Starting date	9 February 2019
Contact information	Dr Marriot Nliwasa; mnliwasa@medcol.mw

ISRCTN77241966 *(Continued)*

Notes	Isrctn.com Identifier: ISRCTN77241966

NCT03154320

Study name	A trial of same-day testing and treatment to improve outcomes among symptomatic patients newly diagnosed with HIV
Target condition and reference standard(s)	Tuberculosis, HIV/AIDS
Index and comparator tests	Spot and early-morning Xpert Ultra results and chest X-ray, as single and as combined tests, with liquid culture as reference standard
Starting date	16 May 2017
Contact information	Serena P Koenig, MD; skoenig@bwh.harvard.edu
Notes	ClinicalTrials.gov Identifier: NCT03154320

NCT03187964

Study name	Xpert Ultra and Xpert HIV-VL in people living with HIV (UltraHIV)
Target condition and reference standard(s)	Tuberculosis, HIV/AIDS
Index and comparator tests	Impact study
Starting date	15 June 2017
Contact information	Grant Theron, PhD; gtheron@sun.ac.za
Notes	ClinicalTrials.gov Identifier: NCT03187964

NCT03356925

Study name	Improving tuberculosis diagnosis and treatment through Basic, Applied and health systems Research (BAR)
Target condition and reference standard(s)	Tuberculosis
Index and comparator tests	Xpert Ultra point-of-care testing compared to the standard-of-care tuberculosis testing at a centralized facility
Starting date	29 November 2017
Contact information	Grant Theron, PhD; gtheron@sun.ac.za
Notes	ClinicalTrials.gov Identifier: NCT03356925

NCT03497195

Study name	Achieving tuberculosis control in Zambia
Target condition and reference standard(s)	Tuberculosis
Index and comparator tests	Comparison of 2 diagnostic tools (chest X-ray with computer-assisted diagnosis versus C-reactive protein) and Xpert Ultra for active community-based tuberculosis case detection
Starting date	13 April 2018
Contact information	Stewart Reid, MD, MPH; stewart.reid@cidrz.org
Notes	ClinicalTrials.gov Identifier: NCT03497195

NCT03712709

Study name	Xpert MTB/XDR Clinical Evaluation Trial
Target condition and reference standard(s)	Tuberculosis, MDR-TB, Xpert MTB/XDR
Index and comparator tests	Index test is Xpert MTB/XDR, with comparators of Xpert MTB/RIF or Ultra.
Starting date	2 November 2018
Contact information	Adam Penn-Nicholson, PhD; adam.penn-nicholson@finddx.org
Notes	ClinicalTrials.gov Identifier: NCT03728725

NCT04074369

Study name	Evaluation of CRISPR-based test for the rapid identification of TB in pulmonary tuberculosis suspects
Target condition and reference standard(s)	Tuberculosis, CRISPR
Index and comparator tests	Index test is CRISPR, with reference standard and comparators to include Xpert MTB/RIF, clinical diagnosis, and culture.
Starting date	30 August 2019
Contact information	Wenhong Zhang; zhangwenhong@fudan.edu.cn
Notes	ClinicalTrials.gov Identifier: NCT04074369

NCT04122404

Study name	POC Strategies to Improve TB Care in Advanced HIV Disease (TBPOC)
Target condition and reference standard(s)	Tuberculosis, HIV/AIDS
Index and comparator tests	Index test is Lateral flow urine lipoarabinomannan (LF-LAM), with comparators including sputum smear microscopy, Xpert MTB/RIF and Xpert MTB/RIF Ultra, and sputum culture.
Starting date	10 October 2019
Contact information	Johanna Maria Åhsberg, MD; johanna.maria.aahsberg@rsyd.dk
Notes	ClinicalTrials.gov Identifier: NCT04122404

NCT058236

Study name	Tuberculosis Research of INA-RESPOND On Drug Resistance (TRIPOD)
Target condition and reference standard(s)	Tuberculosis
Index and comparator tests	Index test is Xpert MTB/RIF and acid-fast bacilli (AFB) smear as compared to sputum culture. Will also evaluate clinical diagnosis as compared to sputum culture.
Starting date	5 May 2016
Contact information	Erlina Burhan, SpP(K), MSc
Notes	ClinicalTrials.gov Identifier: NCT02758236

DATA

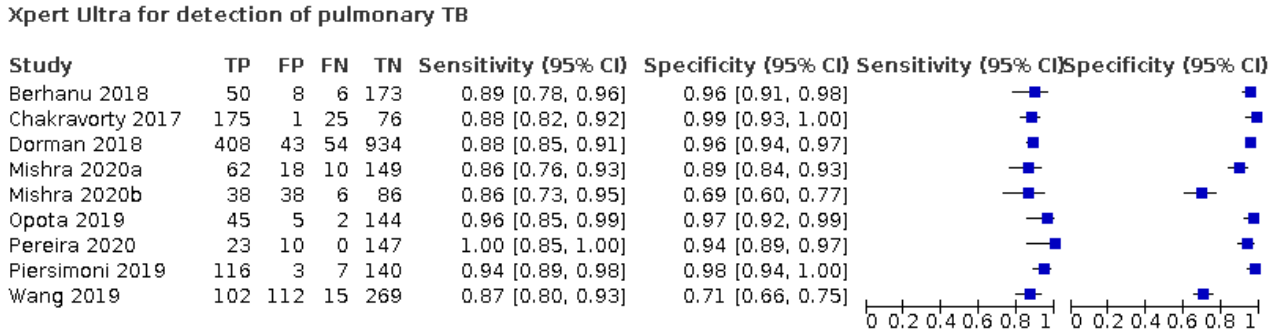
Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Xpert Ultra for detection of pulmonary TB	9	3500
2 Xpert MTB/RIF for detection of pulmonary TB	7	2835
3 Xpert Ultra for detection of pulmonary TB, composite reference standard	2	433
4 Xpert MTB/RIF for detection of pulmonary TB, composite reference standard	2	433
5 Smear-negative, Xpert Ultra, culture	7	2547
6 Smear-negative, Xpert MTB/RIF, culture	7	2549

Test	No. of studies	No. of participants
7 Smear-positive, Xpert Ultra	6	593
8 Smear-positive, Xpert MTB/RIF	6	598
9 HIV-positive, Xpert Ultra	3	627
10 HIV-positive, Xpert MTB/RIF	3	635
11 HIV-negative, Xpert Ultra	3	755
12 HIV-negative, Xpert MTB/RIF	3	755
13 Xpert Ultra, history of TB	4	602
14 Xpert Ultra, no history of TB	3	1476
15 Xpert MTB/RIF, history of TB	4	610
16 Xpert MTB/RIF, no history of TB	3	1476
17 Xpert Ultra for detection of rifampicin resistance	5	921
18 Xpert MTB/RIF for detection of rifampicin resistance	5	930
19 Xpert Ultra repeated test in adults with initial trace result, microbiological reference standard	3	40
20 Xpert Ultra for detection of rifampicin resistance, smear-positive	4	686
21 Xpert MTB/RIF for detection of rifampicin resistance, smear-positive	4	699
22 Xpert Ultra for detection of rifampicin resistance, smear-negative	4	412
23 Xpert MTB/RIF for detection of rifampicin resistance, smear-negative	4	416

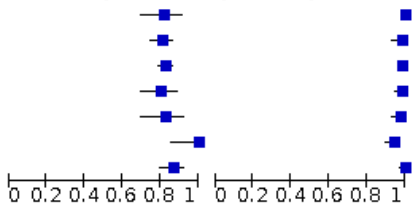
Test 1. Xpert Ultra for detection of pulmonary TB



Test 2. Xpert MTB/RIF for detection of pulmonary TB

Xpert MTB/RIF for detection of pulmonary TB

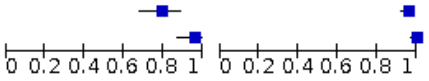
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	46	0	10	181	0.82 [0.70, 0.91]	1.00 [0.98, 1.00]		
Chakravorty 2017	162	1	38	76	0.81 [0.75, 0.86]	0.99 [0.93, 1.00]		
Dorman 2018	383	17	79	960	0.83 [0.79, 0.86]	0.98 [0.97, 0.99]		
Mishra 2020a	58	3	14	164	0.81 [0.70, 0.89]	0.98 [0.95, 1.00]		
Opota 2019	39	4	8	145	0.83 [0.69, 0.92]	0.97 [0.93, 0.99]		
Pereira 2020	23	9	0	148	1.00 [0.85, 1.00]	0.94 [0.89, 0.97]		
Piersimoni 2019	107	0	16	144	0.87 [0.80, 0.92]	1.00 [0.97, 1.00]		



Test 3. Xpert Ultra for detection of pulmonary TB, composite reference standard

Xpert Ultra for detection of pulmonary TB, composite reference standard

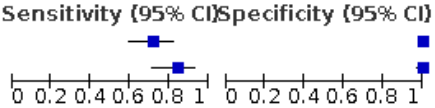
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	51	7	13	166	0.80 [0.68, 0.89]	0.96 [0.92, 0.98]		
Opota 2019	50	0	2	144	0.96 [0.87, 1.00]	1.00 [0.97, 1.00]		



Test 4. Xpert MTB/RIF for detection of pulmonary TB, composite reference standard

Xpert MTB/RIF for detection of pulmonary TB, composite reference standard

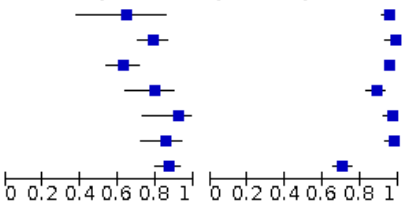
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	46	0	18	173	0.72 [0.59, 0.82]	1.00 [0.98, 1.00]		
Opota 2019	43	0	8	145	0.84 [0.71, 0.93]	1.00 [0.97, 1.00]		



Test 5. Smear-negative, Xpert Ultra, culture

Smear-negative, Xpert Ultra, culture

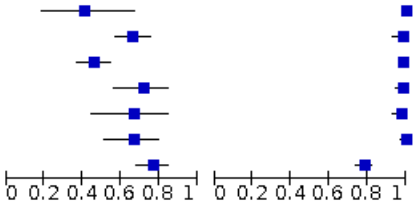
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	11	8	6	173	0.65 [0.38, 0.86]	0.96 [0.91, 0.98]		
Chakravorty 2017	86	1	23	76	0.79 [0.70, 0.86]	0.99 [0.93, 1.00]		
Dorman 2018	86	43	51	931	0.63 [0.54, 0.71]	0.96 [0.94, 0.97]		
Mishra 2020a	34	18	9	144	0.79 [0.64, 0.90]	0.89 [0.83, 0.93]		
Opota 2019	22	5	2	144	0.92 [0.73, 0.99]	0.97 [0.92, 0.99]		
Piersimoni 2019	41	3	7	125	0.85 [0.72, 0.94]	0.98 [0.93, 1.00]		
Wang 2019	102	112	15	269	0.87 [0.80, 0.93]	0.71 [0.66, 0.75]		



Test 6. Smear-negative, Xpert MTB/RIF, culture

Smear-negative, Xpert MTB/RIF, culture

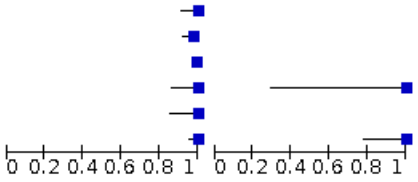
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	7	0	10	181	0.41 [0.18, 0.67]	1.00 [0.98, 1.00]
Chakravorty 2017	73	1	37	76	0.66 [0.57, 0.75]	0.99 [0.93, 1.00]
Dorman 2018	63	17	74	957	0.46 [0.37, 0.55]	0.98 [0.97, 0.99]
Mishra 2020a	31	3	12	159	0.72 [0.56, 0.85]	0.98 [0.95, 1.00]
Opota 2019	16	4	8	145	0.67 [0.45, 0.84]	0.97 [0.93, 0.99]
Piersimoni 2019	32	0	16	129	0.67 [0.52, 0.80]	1.00 [0.97, 1.00]
Wang 2019	90	83	27	298	0.77 [0.68, 0.84]	0.78 [0.74, 0.82]



Test 7. Smear-positive, Xpert Ultra

Smear-positive, Xpert Ultra

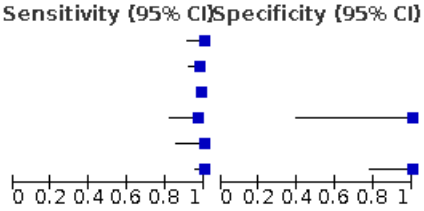
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	39	0	0	0	1.00 [0.91, 1.00]	Not estimable
Chakravorty 2017	88	0	2	0	0.98 [0.92, 1.00]	Not estimable
Dorman 2018	320	0	3	0	0.99 [0.97, 1.00]	Not estimable
Mishra 2020a	25	0	0	3	1.00 [0.86, 1.00]	1.00 [0.29, 1.00]
Opota 2019	23	0	0	0	1.00 [0.85, 1.00]	Not estimable
Piersimoni 2019	75	0	0	15	1.00 [0.95, 1.00]	1.00 [0.78, 1.00]



Test 8. Smear-positive, Xpert MTB/RIF

Smear-positive, Xpert MTB/RIF

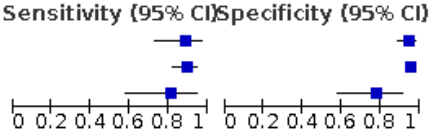
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	39	0	0	0	1.00 [0.91, 1.00]	Not estimable
Chakravorty 2017	88	0	2	0	0.98 [0.92, 1.00]	Not estimable
Dorman 2018	319	0	4	0	0.99 [0.97, 1.00]	Not estimable
Mishra 2020a	28	0	1	4	0.97 [0.82, 1.00]	1.00 [0.40, 1.00]
Opota 2019	23	0	0	0	1.00 [0.85, 1.00]	Not estimable
Piersimoni 2019	75	0	0	15	1.00 [0.95, 1.00]	1.00 [0.78, 1.00]



Test 9. HIV-positive, Xpert Ultra

HIV-positive, Xpert Ultra

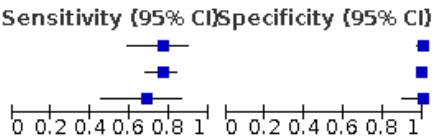
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	30	6	4	107	0.88 [0.73, 0.97]	0.95 [0.89, 0.98]
Dorman 2018	103	14	12	303	0.90 [0.82, 0.94]	0.96 [0.93, 0.98]
Mishra 2020a	17	6	4	21	0.81 [0.58, 0.95]	0.78 [0.58, 0.91]



Test 10. HIV-positive, Xpert MTB/RIF

HIV-positive, Xpert MTB/RIF

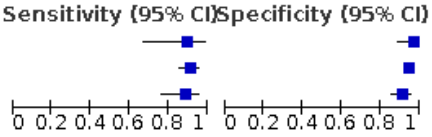
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	26	0	8	113	0.76 [0.59, 0.89]	1.00 [0.97, 1.00]
Dorman 2018	88	2	27	315	0.77 [0.68, 0.84]	0.99 [0.98, 1.00]
Mishra 2020a	15	0	7	34	0.68 [0.45, 0.86]	1.00 [0.90, 1.00]



Test 11. HIV-negative, Xpert Ultra

HIV-negative, Xpert Ultra

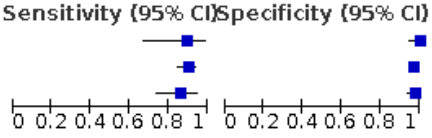
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	17	2	2	61	0.89 [0.67, 0.99]	0.97 [0.89, 1.00]
Dorman 2018	145	17	14	307	0.91 [0.86, 0.95]	0.95 [0.92, 0.97]
Mishra 2020a	45	12	6	127	0.88 [0.76, 0.96]	0.91 [0.85, 0.95]



Test 12. HIV-negative, Xpert MTB/RIF

HIV-negative, Xpert MTB/RIF

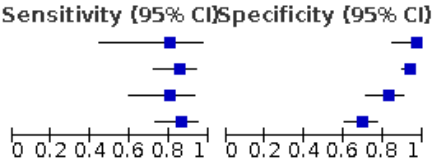
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	17	0	2	63	0.89 [0.67, 0.99]	1.00 [0.94, 1.00]
Dorman 2018	143	9	16	315	0.90 [0.84, 0.94]	0.97 [0.95, 0.99]
Mishra 2020a	44	3	7	136	0.86 [0.74, 0.94]	0.98 [0.94, 1.00]



Test 13. Xpert Ultra, history of TB

Xpert Ultra, history of TB

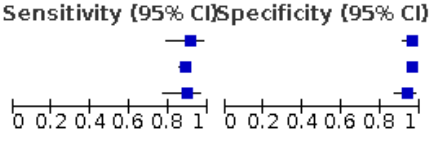
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	8	1	2	32	0.80 [0.44, 0.97]	0.97 [0.84, 1.00]
Dorman 2018	41	17	7	232	0.85 [0.72, 0.94]	0.93 [0.89, 0.96]
Mishra 2020a	20	12	5	57	0.80 [0.59, 0.93]	0.83 [0.72, 0.91]
Mishra 2020b	38	38	6	86	0.86 [0.73, 0.95]	0.69 [0.60, 0.77]



Test 14. Xpert Ultra, no history of TB

Xpert Ultra, no history of TB

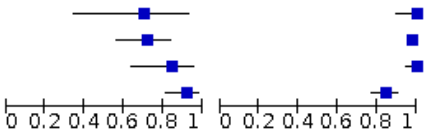
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	41	6	4	139	0.91 [0.79, 0.98]	0.96 [0.91, 0.98]
Dorman 2018	367	26	47	701	0.89 [0.85, 0.92]	0.96 [0.95, 0.98]
Mishra 2020a	42	6	5	92	0.89 [0.77, 0.96]	0.94 [0.87, 0.98]



Test 15. Xpert MTB/RIF, history of TB

Xpert MTB/RIF, history of TB

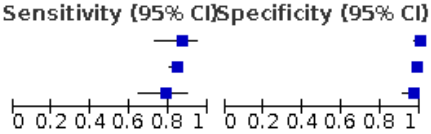
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	7	0	3	33	0.70 [0.35, 0.93]	1.00 [0.89, 1.00]		
Dorman 2018	33	5	13	244	0.72 [0.57, 0.84]	0.98 [0.95, 0.99]		
Mishra 2020a	21	0	4	69	0.84 [0.64, 0.95]	1.00 [0.95, 1.00]		
Mishra 2020b	47	20	4	107	0.92 [0.81, 0.98]	0.84 [0.77, 0.90]		



Test 16. Xpert MTB/RIF, no history of TB

Xpert MTB/RIF, no history of TB

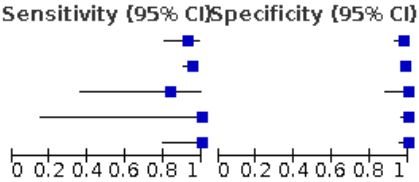
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Berhanu 2018	39	0	6	145	0.87 [0.73, 0.95]	1.00 [0.97, 1.00]		
Dorman 2018	348	12	66	715	0.84 [0.80, 0.87]	0.98 [0.97, 0.99]		
Mishra 2020a	37	3	10	95	0.79 [0.64, 0.89]	0.97 [0.91, 0.99]		



Test 17. Xpert Ultra for detection of rifampicin resistance

Xpert Ultra for detection of rifampicin resistance

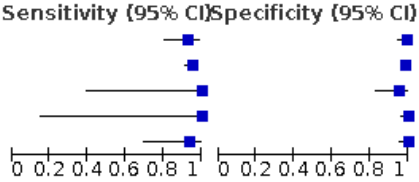
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	38	2	3	96	0.93 [0.80, 0.98]	0.98 [0.93, 1.00]		
Dorman 2018	166	6	9	370	0.95 [0.90, 0.98]	0.98 [0.97, 0.99]		
Mishra 2020b	5	0	1	28	0.83 [0.36, 1.00]	1.00 [0.88, 1.00]		
Piersimoni 2019	2	0	0	105	1.00 [0.16, 1.00]	1.00 [0.97, 1.00]		
Wang 2019	16	0	0	74	1.00 [0.79, 1.00]	1.00 [0.95, 1.00]		



Test 18. Xpert MTB/RIF for detection of rifampicin resistance

Xpert MTB/RIF for detection of rifampicin resistance

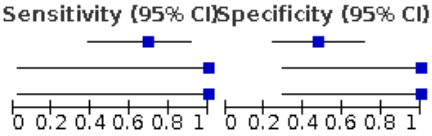
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	38	1	3	97	0.93 [0.80, 0.98]	0.99 [0.94, 1.00]		
Dorman 2018	167	7	8	369	0.95 [0.91, 0.98]	0.98 [0.96, 0.99]		
Mishra 2020b	4	2	0	37	1.00 [0.40, 1.00]	0.95 [0.83, 0.99]		
Piersimoni 2019	2	0	0	105	1.00 [0.16, 1.00]	1.00 [0.97, 1.00]		
Wang 2019	15	0	1	74	0.94 [0.70, 1.00]	1.00 [0.95, 1.00]		



Test 19. Xpert Ultra repeated test in adults with initial trace result, microbiological reference standard

Xpert Ultra repeated test in adults with initial trace result, microbiological reference standard

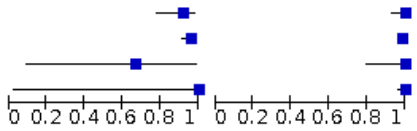
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	9	10	4	9	0.69 [0.39, 0.91]	0.47 [0.24, 0.71]		
Mishra 2020a	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]		
Piersimoni 2019	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]		



Test 20. Xpert Ultra for detection of rifampicin resistance, smear-positive

Xpert Ultra for detection of rifampicin resistance, smear-positive

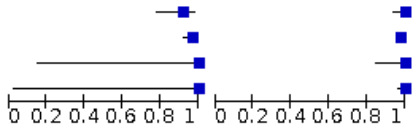
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	34	0	3	50	0.92 [0.78, 0.98]	1.00 [0.93, 1.00]		
Dorman 2018	144	6	6	319	0.96 [0.91, 0.99]	0.98 [0.96, 0.99]		
Mishra 2020b	2	0	1	16	0.67 [0.09, 0.99]	1.00 [0.79, 1.00]		
Piersimoni 2019	1	0	0	104	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]		



Test 21. Xpert MTB/RIF for detection of rifampicin resistance, smear-positive

Xpert MTB/RIF for detection of rifampicin resistance, smear-positive

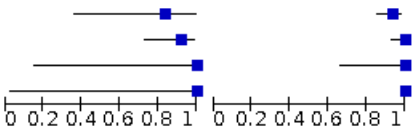
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	34	0	3	57	0.92 [0.78, 0.98]	1.00 [0.94, 1.00]		
Dorman 2018	145	7	5	319	0.97 [0.92, 0.99]	0.98 [0.96, 0.99]		
Mishra 2020b	2	0	0	22	1.00 [0.16, 1.00]	1.00 [0.85, 1.00]		
Piersimoni 2019	1	0	0	104	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]		



Test 22. Xpert Ultra for detection of rifampicin resistance, smear-negative

Xpert Ultra for detection of rifampicin resistance, smear-negative

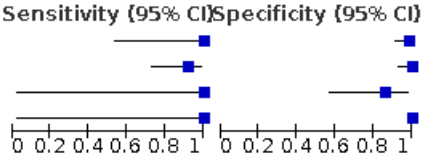
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	5	4	1	62	0.83 [0.36, 1.00]	0.94 [0.85, 0.98]		
Dorman 2018	22	0	2	51	0.92 [0.73, 0.99]	1.00 [0.93, 1.00]		
Mishra 2020b	2	0	0	9	1.00 [0.16, 1.00]	1.00 [0.66, 1.00]		
Piersimoni 2019	1	0	0	253	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]		



Test 23. Xpert MTB/RIF for detection of rifampicin resistance, smear-negative

Xpert MTB/RIF for detection of rifampicin resistance, smear-negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	6	1	0	63	1.00 [0.54, 1.00]	0.98 [0.92, 1.00]		
Dorman 2018	22	0	2	53	0.92 [0.73, 0.99]	1.00 [0.93, 1.00]		
Mishra 2020b	1	2	0	12	1.00 [0.03, 1.00]	0.86 [0.57, 0.98]		
Piersimoni 2019	1	0	0	253	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]		



ADDITIONAL TABLES

Table 1. Summary of key study characteristics

Study, year ID	Country	Study design	Number of participants	Age (mean or median; years)	Female sex	HIV-positive	History of tuberculosis	Pulmonary tuberculosis reference standard	Rifampicin resistance reference standard
Berhanu 2018	South Africa	Prospective cohort	237	36	33%	62%	18%	LJ and MGIT; composite	LJ, MGIT, and MTBDR*plus*
Chakravorty 2017	FIND biobank frozen specimens (Peru, Vietnam, South Africa) and clinical specimens (Georgia, India)	Cross-sectional	277	Not reported	Not reported	Not reported	Not reported	LJ and MGIT	LJ and MGIT
Dorman 2018	Belarus, Brazil, China, Georgia, India, Kenya, South Africa, Uganda	Prospective cohort	1439 for detection of MTB, 551 for detection of rifampicin resistance	28	40%	44%	21%	LJ and MGIT	LJ and MGIT
Mishra 2020a	South Africa	Prospective cohort	239	37	49%	20%	39%	MGIT	MTBDR*plus*
Mishra 2020b	South Africa	Cross-sectional	346	38	40%	44%	100%	MGIT	MTBDR*plus*
Opota 2019	Switzerland	Cross-sectional	196	Not reported	Not reported	Not reported	Not reported	MGIT; composite	MGIT
Pereira 2020	Brazil	Cross-sectional	180	50	44%	2%	0%	Ogawa-Kudoh	N/A
Piersimoni 2019	Italy	Cross-sectional	266	42	37%	Not reported	Excluded	MGIT	MGIT
Wang 2019	China	Prospective cohort	498	47	34%	0%	50%	LJ and MGIT	LJ

Abbreviations: FIND: Foundation for Innovative New Diagnostics; LJ: Löwenstein–Jensen; MGIT: Mycobacteria Growth Indicator Tube; MTB; *Mycobacterium tuberculosis;* N/A: not applicable.

Table 2. Xpert Ultra and Xpert MTB/RIF for the detection of pulmonary tuberculosis and rifampicin resistance

Test (analysis)	Reference standard	No. studies (participants)	No. (%) with pulmonary TB or rifampicin resistance	Median pooled sensitivity (95% CrI)	Median pooled specificity (95% CrI)	Positive predictive value (95% CrI) *	Negative predictive value (95% CrI)
Xpert Ultra, unselected participants* (pulmonary tuberculosis detection)	Culture	7 (2834)**	983 (34.7%)	90.9% (86.2 to 94.7)	95.6% (93.0 to 97.4)	69.6% (58.7 to 79.8)	99.0% (98.4 to 99.4)
Xpert MTB/RIF (pulmonary tuberculosis detection)	Culture	7 (2835)	983 (34.7%)	84.7% (78.6 to 89.9)	98.4% (97.0 to 99.3)	85.4% (75.8 to 93.1)	98.3% (97.6 to 98.9)
Xpert Ultra (rifampicin resistance detection)	DST, line probe assays	5 (921)	240 (26.1%)	94.9% (88.9 to 97.9)	99.1% (97.7 to 99.8)	91.7% (82.1 to 97.4)	99.4% (98.7 to 99.8)
Xpert MTB/RIF (rifampicin resistance detection)	DST, line probe assays	5 (930)	238 (25.6%)	95.3% (90.0 to 98.1)	98.8% (97.2 to 99.6)	99.5% (98.9 to 99.8)	99.4% (98.7 to 99.8)

Abbreviations: CrI: credible interval; DST: drug susceptibility testing with solid or liquid culture methods
* Positive and negative predictive values were determined at a pretest probability of 10%
**This analysis included studies that did not preselect participants based on microcopy results or those who had received previous antituberculosis treatment.
***Piersimoni 2019 reported three non-determinate results for Xpert Ultra and two for Xpert MTB/RIF, accounting for the small difference in the total number of participants in this analysis.

Table 3. Comparative accuracy of Xpert Ultra and Xpert MTB/RIF*

Detection of pulmonary tuberculosis				
Test (studies, participants)	Xpert Ultra (7, 2834)	Xpert MTB/RIF (7, 2835)	Difference (Xpert Ultra minus Xpert MTB/RIF)*	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	90.9% (86.2 to 94.7)	84.7% (78.6 to 89.9)	6.3% (0.1 to 12.8)	0.98
Specificity (95% CrI)	95.6% (93.0 to 97.4)	98.4% (97.0 to 99.3)	−2.7% (−5.7 to −0.5)	0.01
Smear-positive (tuberculosis detection)				
Test (studies, participants)	Xpert Ultra (6, 593)	Xpert MTB/RIF (6, 598)	Difference (Xpert Ultra minus Xpert MTB/RIF)**	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	99.3% (98.1 to 99.8)	98.9% (97.5 to 99.6)	0.3% (−1.0 to 1.8)	0.72
Specificity (95% CrI)	Not estimated	Not estimated	N/A	N/A
Smear-negative (tuberculosis detection)				
Test (studies, participants)	Xpert Ultra (6, 2049)	Xpert MTB/RIF (6, 2051)	Difference (Xpert Ultra minus Xpert MTB/RIF)**	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	77.5% (67.6 to 85.6)	60.6% (48.4 to 71.7)	16.7% (2.1 to 31.8)	1.00
Specificity (95% CrI)	95.8% (92.9 to 97.7)	98.8% (97.7 to 99.5)	−3.0% (-5.9 to −0.9)	0.00
History of tuberculosis				
Test (studies, participants)	Xpert Ultra (4, 602)	Xpert MTB/RIF (4, 610)	Difference (Xpert Ultra minus Xpert MTB/RIF)*	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	84.2% (72.5 to 91.7)	81.8% (68.7 to 90.0)	2.4% (−11.9 to 17.2)	0.64
Specificity (95% CrI)	88.2% (70.5 to 96.6)	97.4% (91.7 to 99.5)	−8.9% (−27.0 to 0.6)	0.03
Detection of rifampicin resistance				
Test (studies, participants)	Xpert Ultra (5, 921)	Xpert MTB/RIF (5, 930)	Difference (Xpert Ultra minus Xpert MTB/RIF)**	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	94.9% (88.9 to 97.9)	95.3% (90.0 to 98.1)	−0.3% (−6.9 to 5.7)	0.45
Specificity (95% CrI)	99.1% (97.7 to 99.8)	98.8% (97.2 to 99.6)	0.3% (−1.2 to 2.0)	0.67
Smear-positive (rifampicin resistance detection)				
Test (studies, participants)	Xpert Ultra (4, 686)	Xpert MTB/RIF (4, 699)	Difference (Xpert Ultra minus Xpert MTB/RIF)**	Probability (Xpert Ultra minus Xpert MTB/RIF)

Table 3. Comparative accuracy of Xpert Ultra and Xpert MTB/RIF* *(Continued)*

Sensitivity (95% CrI)	93.9% (84.4 to 97.7)	95.5% (88.4 to 98.6)	−1.5% (−10.9 to 6.0)	0.32
Specificity (95% CrI)	99.3% (97.8 to 99.9)	99.1% (97.3 to 99.9)	0.1% (−1.5 to 2.0)	0.59
Smear-negative (rifampicin resistance detection)				
Test (studies, participants)	Xpert Ultra (4, 412)	Xpert MTB/RIF (4, 416)	Difference (Xpert Ultra minus Xpert MTB/RIF)**	Probability (Xpert Ultra minus Xpert MTB/RIF)
Sensitivity (95% CrI)	92.0% (75.0 to 95.8)	95.4% (82.3 to 99.3)	−3.1% (−20.7 to 11.7)	0.30
Specificity (95% CrI)	99.4% (96.2 to 100)	99.2% (94.8 to 100)	0.1% (−3.0 to 4.5)	0.58

Abbreviations: CrI: credible interval
* We determined absolute differences for sensitivity and specificity when there were at least four studies in a subgroup.
** Slight differences in numerical values are likely due to rounding errors.

Table 4. Xpert Ultra and Xpert MTB/RIF accuracy, analyses in HIV-positive and HIV-negative people

Analysis	Test	No. of studies (participants)	Median pooled sensitivity (95% CrI)	Median pooled specificity (95% CrI)	Positive predictive value (95% CI) *	Negative predictive value (95% CI)
HIV-negative	Xpert Ultra	3 (755)	90.3% (80.3 to 95.6)	94.3% (79.8 to 98.7)	63.5% (45.6 to 79.7)	98.9% (97.7 to 99.5)
HIV-negative	Xpert MTB/RIF	3 (755)	89.0% (78.3 to 94.8)	98.1% (95.3 to 99.4)	83.8% (67.6 to 94.0)	98.8% (97.6 to 99.4)
HIV-positive	Xpert Ultra	3 (627)	87.6% (75.4 to 94.1)	92.8% (82.3 to 97.0)	57.4% (34.5 to 76.8)	98.5% (97.0 to 99.3)
HIV-positive	Xpert MTB/RIF	3 (635)	74.9% (58.7 to 86.2)	99.7% (98.6 to 100.0)	96.3% (85.4 to 99.6)	97.3% (95.6 to 98.5)

Abbreviations: CI: confidence interval; CrI: credible interval
* Positive and negative predictive values were determined at a pretest probability of 10%

Table 5. Summary of Xpert Ultra trace-positive results

Study	Country	Culture-positive MTB/total	Trace results (% of Ultra positive)	Number (%) of trace results with history of tuberculosis	Culture-positive trace/total trace	Additional testing on trace results (not including retesting)	Trace results repeated?
Berhanu 2018	South Africa	56/237	6 (10.3%)	1/5 (20.0%); this 1 patient was culture positive	2/6	Sputum re-collected at day 60 in 1 participant was MGIT negative.	No
Chakravorty 2017	FIND biobank samples (Peru, Vietnam, South Africa) and clinical samples (Georgia, India)	200/277	Not reported	-	-	-	No
Dorman 2018	Belarus, Brazil, China, Georgia, India, Kenya, South Africa, Uganda	462/1439	32 (7.1%)	Of 19 culture-negative trace results, 11 (57.9%) had history of TB.	13/32	Among culture-negative, a follow-up culture at 2 months was positive in 2/10.	Yes: 13 of the retested samples were culture+; of these 9 were Ultra + on repeat. 19 of the samples were culture-, of which 10 were Ultra false +
Mishra 2020a	South Africa	72/239	13 (18.6%)	6/13 (46.2%)	4/13	-	Yes: new sample collected median 444 days, after the initial testing. 4 samples retested (1 culture+, 3 culture-); all culture- were not detected, and culture+ was Ultra +
Mishra 2020b	South Africa	44/168	21 (27.6%)	21/21 (100%)	2/21	-	No
Opota 2019	Switzerland	47/196	5 (10.0%)	Not reported	4/5	The 1 culture-negative patient was culture-positive on a lymph node specimen.	No
Pereira 2020	Brazil	157/180	1 (3.0%)	Not reported	Not reported	-	No

Table 5. Summary of Xpert Ultra trace-positive results *(Continued)*

Piersimoni 2019	Italy	123/266	8 (6.7%)	Excluded from study	5/8	-	Yes: 4 respiratory samples retested (1 culture+, 3 culture-); all culture- were not detected, and culture+ was Ultra +
Wang 2019	China	117/498	65 (30.4%)	Not reported	Not reported	-	No

Abbreviations: FIND: Foundation for Innovative New Diagnostics; MGIT: Mycobacteria Growth Indicator Tube; MTB: *Mycobacterium tuberculosis*; TB: tuberculosis
- Could not determine

Table 6. Sensitivity analyses, Xpert Ultra

Type of analysis (no. of studies, participants)	Median pooled sensitivity (95% CrI)	Median pooled specificity (95% CrI)	Positive predictive value (95% CrI)	Negative predictive value (95% CrI)
Xpert Ultra sensitivity and specificity for pulmonary tuberculosis detection in studies with unselected patients (7, 2834)	90.9% (86.2 to 94.7)	95.6% (93.0 to 97.4)	69.6% (58.7 to 79.8)	99.0% (98.4 to 99.4)
Studies that only included untreated participants (exclude studies with some percentage of participants who were receiving tuberculosis treatment) (5, 2361)	90.9% (84.7 to 95.3)	94.9% (91.3 to 97.2)	66.4% (53.2 to 78.4)	98.9% (98.2 to 99.5)
Studies that used liquid culture only as the reference standard for tuberculosis detection (4, 978)	91.1% (84.0 to 95.5)	96.1% (91.7 to 98.5)	72.1% (54.5 to 87.2)	99.0% (98.2 to 99.5)
Studies where consecutive or random participants were selected (6, 2557)	91.6% (86.6 to 95.4)	95.3% (92.4 to 97.2)	68.2% (56.9 to 78.5)	99.0% (98.5 to 99.5)
Studies where the reference standard was blinded (6, 2654)	90.2% (85.2 to 93.8)	95.9% (93.0 to 97.7)	70.8% (58.5 to 81.8)	98.9% (98.3 to 99.3)
Studies using fresh specimens (4, 2095)	89.8% (82.1 to 95.1)	94.1% (89.3 to 96.8)	62.7% (47.9 to 75.8)	98.8% (97.9 to 99.4)

Abbreviations: CrI: credible interval.

Table 7. Selected systematic reviews on the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance

Author, year (see descriptions of systematic reviews in footnotes)	Date searched up to	No. of studies (participants)	Test	Pulmonary tuberculosis, summary estimates (95% CI)*		No. of studies	Rifampicin resistance, summary estimates (95% CrI)*	
				Sensitivity	Specificity		Sensitivity	Specificity
Chang 2012	October 2011	15 (8117)	Xpert MTB/RIF	90% (89 to 91)	98% (98 to 99)	7	See footnote for this study	See footnote for this study
Walusimbi 2013 (smear-negative)	May 2012	15 (2046)	Xpert MTB/RIF	67% (62 to 71)	98% (97 to 99)	N/A	N/A	N/A
Steingart 2014	December 2013	27 (6026)	Xpert MTB/RIF	89% (85 to 92)	99% (98 to 99)	Sensitivity: 17 Specificity: 24	95% (90 to 97)	98% (97 to 99)
Yan 2016	Not reported	12 (8122)	Xpert MTB/RIF	89% (87 to 90)	98% (98 to 99)	N/A	N/A	N/A
Li 2017	June 2015	24 (2486)	Xpert MTB/RIF	87% (83 to 90)	97% (96 to 98)	N/A	N/A	N/A
Alvis-Zakzuk 2017	December 2015	N/A	Xpert MTB/RIF	N/A	N/A	8	See footnote for this study	See footnote for this study
Horne 2019	January 2018	85 (41,965)	Xpert MTB/RIF	85% (82 to 87)	98% (97 to 98)	48 (8020)	96% (94 to 97)	98% (98 to 99)
Zhang 2019	May 2019	10 (not reported)	Xpert Ultra	89% (82 to 94)	97% (95 to 98)	4 (856)	95% (92 to 97)	99% (98 to 100)
Jiang 2020	April 2020	19 (5855)	Xpert Ultra and Xpert MTB/RIF	Xpert MTB/RIF: 69% (57 to 78) Xpert Ultra: 84% (76 to 90)	Xpert MTB/RIF: 99% (98 to 99) Xpert Ultra: 97% (96 to 98)	N/A	N/A	N/A

Abbreviations: CI: confidence interval; CrI: credible interval; N/A: not applicable.

*Summary sensitivity and specificity estimates are provided for Xpert MTB/RIF, except for Zhang 2019 and Jiang 2020, which evaluated Xpert Ultra.
Chang 2012 included adults and children; Xpert MTB/RIF for detection of rifampicin resistance, sensitivity range 17% to 100%, specificity range 72% to 100%.
Walusimbi 2013 only included smear-negative participants.
Steingart 2014 is a previous Cochrane Review.
Yan 2016 only included studies that provided data by smear and HIV status.
Li 2017 106 studies (52,410 specimens) for both pulmonary and extrapulmonary tuberculosis.
Alvis-Zakzuk 2017 summarized accuracy of Xpert MTB/RIF for the detection of rifampicin resistance, sensitivity range 33% to 100%, specificity range 91% to 100%.
Horne 2019 is a previous Cochrane Review update.
Zhang 2019 included adults and children.
Jiang 2020 included adults and children, and assessed Xpert Ultra and Xpert MTB/RIF accuracy for the detection of both pulmonary and extrapulmonary tuberculosis.
Systematic reviews not included in this table:
Kaur 2016 did not provide summary sensitivity and specificity estimates.
Lange 2017 provided sensitivity and specificity with respect to Xpert cycle threshold (C_T) values.
Maynard-Smith 2014 provided accuracy estimates for pulmonary tuberculosis on gastric aspirates and stool.
Wang 2015 only included children.

Table 8. Prespecified changes for 2021 review update*

Protocol section	Refreshed protocol
Background and research question	This review update will describe the burden of pulmonary tuberculosis worldwide based on the latest World Health Organization (WHO) Global Tuberculosis Report. The Background will describe the updated WHO guidelines on molecular methods for diagnosing tuberculosis, including Xpert MTB/RIF and Xpert Ultra. The WHO Meeting to update the guidelines will take place 3 to 6 December 2019. This Cochrane Review update will have informed these guidelines.
Inclusion criteria	This is a diagnostic test accuracy review. Participants, index tests, and target condition will be the same as in Horne 2019. We will add a composite reference standard for Xpert Ultra defined as culture or clinical criteria as defined by the primary study authors, or both. The primary objectives are to assess the diagnostic accuracy of Xpert Ultra for the diagnosis of pulmonary tuberculosis and to assess the diagnostic accuracy of Xpert Ultra for the diagnosis rifampicin resistance in adults. Secondary objectives are as follows: • to investigate potential sources of heterogeneity in test accuracy, including history of tuberculosis and smear and HIV status; • to compare the accuracy of Xpert Ultra and Xpert MTB/RIF in studies that evaluated both tests. Concerning patient outcomes, the Discussion will summarize and refer to key findings in the test-treatment Cochrane Review by Haraka 2018.
Methods	We will use QUADAS-2 to appraise methodological quality of the included studies, consistent with Horne 2019. If there are sufficient data, we will perform meta-analyses using a bivariate random-effects model. The analyses will include: • Xpert Ultra for pulmonary tuberculosis, culture reference standard; • Xpert Ultra for pulmonary tuberculosis, composite reference standard; • accuracy of Xpert Ultra versus Xpert MTB/RIF in studies that evaluated both tests; • Xpert Ultra for pulmonary tuberculosis, smear-positive; • Xpert Ultra for pulmonary tuberculosis, smear-negative, culture positive; • Xpert Ultra for pulmonary tuberculosis, HIV-positive; • Xpert Ultra for pulmonary tuberculosis in participants with a history of tuberculosis; • Xpert Ultra for detecting rifampicin resistance. We will create 'Summary of findings' tables for the two primary objectives of the review.

*This table was approved by the Cochrane Infectious Diseases Group editorial team on 23 October 2019.

APPENDICES

Appendix 1. Search strategy

MEDLINE (OVID) and Embase (OVID)

1. (tuberculosis or TB).tw

limit 1 to yr="2007 -Current"

2. Mycobacterium tuberculosis/

limit 2 to yr="2007 -Current"

3. Tuberculosis, Multidrug-Resistant/ or Tuberculosis/ or Tuberculosis, Pulmonary/

limit 3 to yr="2007 -Current"

4. 1 or 2 or 3

5. (Xpert or GeneXpert or cepheid or(near* patient)). tw.

limit 4 to yr="2007 -Current"

4 and 5

Web of Knowledge (SCI-expanded, SSCI, Conference Proceedings science, BIOSIS previews)

(tuberculosis OR TB OR mycobacterium) (topic) AND (Xpert OR Genexpert OR cepheid) (topic)

LILACS

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

SCOPUS

(tuberculosis OR TB OR mycobacterium) (title, abstract, keywords) AND (xpert OR Genexpert OR Cepheid) (title, abstract, keywords)

Appendix 2. Data extraction form

I. ID	
ID substudy (for study centres: a, b, c, etc.)	
First author	
Corresponding author and email	
Was author contacted?	1 – Yes 2 – No If yes, dates(s)
Title	
Year (of publication)	
Year (study start date)	
Language	1 – English 2 – Other If other, specify:
II. Study details	
Country where study was conducted	
Country World Bank Classification	1 – Low income 2 - Middle income 3 – High income 4 - Low and high income

(Continued)

	5 - Low and middle income 6 - Low, middle, and high 7 – Other combination, describe
Purpose of testing as described in the study	1 - Diagnosis 2 - Screening in HIV-positive people 9 - Could not tell Study states:
Objective of study	1 - Detection of PTB only 2 - Detection of rifampicin resistance only 3 - Both, detection of PTB and rifampicin resistance
Study design	1 – Randomized controlled trial 2 – Cross-sectional 3 – Cohort 4 – Other, specify 9 – Could not tell If other, describe:
IIa. Questions about preselection during enrolment	
Were patients preselected based upon microscopy results?	1 - Yes 2 - No 9 - Unknown/NR
If yes, what was the basis for preselection?	1 - Primarily or exclusively smear positive 2 - Primarily or exclusively smear negative 8 - Not applicable
Did study include exclusively retreatment patients upon enrolment? (for example, patients who previously received first-line drugs and those with non-converting pulmonary tuberculosis who were receiving therapy)	1 - Yes 2 - No 9 - Unknown/NR
Participant selection	1 – Consecutive 2 – Random 3 – Convenience 7 – Other

(Continued)

	9 – Unknown/NR
Direction of study data collection	1 – Prospective 2 – Retrospective 9 – Unknown/NR
Number included after recruitment by inclusion and exclusion criteria	_____ 9 – Unknown/NR
Number included in analysis (# recruited − # withdrawals)	_____ 9 – Unknown/NR
Unit of analysis	1 – Patient (with a single Xpert per patient) 2 – Specimen (there are more specimens than patients) 9 – Unknown/NR Describe as in paper, if unclear:
Comments about study design	
III. Patient characteristics and setting	
Presenting signs and symptoms	
Did the study avoid inappropriate exclusions? Please list exclusions noted in study, if any (for example, study includes predominantly or exclusively smear-positive or "difficult-to-diagnose" patients)	1 - Yes 2 - No 9 - Unknown/NR Describe exclusions as stated in study:
Type of specimen (may include expectorated, induced, bronchial alveolar lavage (BAL), tracheal aspirates) (check all that apply). Assume expectorated sputum if not specifically stated.	1 – Expectorated sputum 2 – Induced sputum 3 – Bronchial alveolar lavage or bronchial aspirates 4 – Tracheal aspirates 6 – Other 9 – Unknown/NR If other, describe types and record numbers:
Clinical setting; describe as written in the paper	1 – Outpatient 2 - Inpatient 3 – Both out- and inpatient 4 – Other, specify 5 – Laboratory based 9 – Unknown/NR

(Continued)

	Describe as in paper:
Was Xpert testing performed at point of care? *(POCT is diagnostic testing that will result in a clear and actionable management decision (e.g. start of treatment, referral, initiation of confirmatory test) within the same clinical encounter (e.g. same day). POCT should be mentioned in the study, as it is unlikely if testing takes place in a central level laboratory.)*	1 - Yes 2 - No 9 - Could not tell
Level of the laboratory system where Xpert tests were performed *(Tests generally available at different laboratory levels, though tests may overlap)* *Central: Intermediate laboratory tests and culture on liquid media and DST (1st- and 2nd-line antituberculosis drugs) on solid or in liquid media and line probe assay (LPA) on positive cultures and rapid speciation tests* *Intermediate: Peripheral laboratory tests and culture on solid media and LPA from smear-positive sputum* *Peripheral: AFB (Ziehl-Neelsen, Auramine-rhodamine, Auramine-O staining) and Xpert MTB/RIF*	1- Central 2 - Intermediate 3 - Peripheral 4- Other, specify Describe as in paper:
IV. Other demographics	
Age (range, mean (SD), median (IQR))	9 - Unknown/NR
##/total and % female	9 - Unknown/NR
HIV status of participants	0 - HIV - 1 - HIV + 2 - Both HIV+/- 9 - Unknown/NR
If HIV-positive participants included, what is the percentage?	% (specify numerator/denominator)
Tuberculosis history: Did the study include patients with a history of tuberculosis?	1 - Yes 2 - No

(Continued)

	9 - Unknown/NR
If so, what is the percentage?	% (specify numerator/denominator) 9 - Unknown/NR (for data entry write "NR")
Prior treatment: Did the study include patients with prior tuberculosis treatment?	1 - Yes 2 - No 9 - Unknown/NR
If so, what is the percentage?	% (specify numerator/denominator) 9 - Unknown/NR (for data entry write "NR")
Current treatment: Were patients on treatment (defined as tuberculosis drugs for greater than 7 days) for the current tuberculosis episode? *(note: may impact culture results)*	1 - Yes 2 - No 9 - Unknown/NR
If so, what is the percentage?	% (specify numerator/denominator) 9 - Unknown/NR (for data entry write "NR")
V. Index test	
Xpert version(s) evaluated	1 - Xpert MTB/RIF only 2 - Xpert Ultra only 3 - Any combination Xpert MTB/RIF and Xpert Ultra
Xpert platform: Was Omni used? Unless Omni explicitly described, assume standard platform	1 – Yes, only Omni used for Xpert tests 2 – Yes, both Omni and standard platform used for Xpert tests 3 - No
Was the index test result interpreted without knowledge of the result of the reference standard result?	1 - Yes (since Xpert is automated, we will answer 'Yes" for all studies)
VI. Reference standard	
For tuberculosis detection, what reference standard(s) was used?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 9 – Unknown/NR 1a - Solid culture LJ 7H10 7H11

(Continued)

	Other 9 - Unknown/NR 2a – Liquid culture MGIT 960 Other (specify): 9 - Unknown/NR
For MGIT only, if *more than one specimen* was inoculated for culture, were these specimens obtained on *different days?*	1 – Yes 2 – No 8 – Not applicable 9 – Unknown/NR
For rifampicin resistance detection, what reference standard(s) was used?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 4 - Line probe assays, MTBDR*plus* (specify other) 5 - Other, specify 9 – Unknown/NR 1a - Solid culture LJ 7H10 7H11 Other Specify method, e.g. proportion 2a – Liquid culture MGIT 960 Other (specify)
Tuberculosis detection: Was the reference standard result interpreted without knowledge of the index test result? Answer yes for MGIT	1 – Yes 2 – No 9 – Unknown/NR
Did the study speciate mycobacteria isolated in culture?	1 – Yes 2 – No 9 – Unknown/NR
Rifampicin resistance detection: Was the reference standard result interpreted without knowledge of the index test result? Answer yes for MGIT	1 – Yes 2 – No 9 – Unknown/NR
VII. Specimen flow	
Were Xpert sample and culture obtained from same specimen?	1 – Yes

(Continued)

	2 – No 9 – Unknown/NR
What specimen processing procedure was used before testing with Xpert?	1 – None 2 – NALC-NaOH 3 – NaOH (Petroff) 4 – Other 9 – Unknown/NR
Was microscopy used?	1 – Yes 2 – No 9 – Unknown/NR
Type of microscopy used	1 – Ziehl-Neelsen 2 – Fluorescence microscopy 3 - Both Ziehl-Neelsen and fluorescence microscopy 9 – Unknown/NR
Smear type (if study used both direct and concentrated, select concentrated)	1 – Direct 2 – Concentrated (processed) 9 – Unknown/NR
For Xpert specimen, what was the condition of the specimen when tested?	1 – Fresh 2 – Frozen 3 - Both fresh and frozen 9 – Unknown/NR
VIII. Results	
Did the study report % contaminated cultures? (Enter percentage contaminated cultures, if provided): # of contaminated cultures/Total # cultures performed = %	1 – Yes -> % contaminated cultures: 2 – No
Did the study report the number of non-determinate results for Xpert for tuberculosis detection? (invalid, error, no result) *The* non-determinate *rate for detection of PTB is the number of tests classified as "invalid", "error", or "no result" divided by the total number of Xpert tests performed.*	1 – Yes -> # non-determinate results: Denominator is total number of Xpert tests performed (add total from Table 1 plus # of non-determinate results): 2 – No
Did the study report the number of indeterminate results for Xpert for rifampicin resistance detection? *The indeterminate rate for detection of rifampicin resistance was the number of tests classified as "MTB detected; Rif resistance INDETERMINATE" divided by the total number of Xpert-MTB positive results.*	1 – Yes ->\# indeterminate results: (Enter 0 indeterminate results if the total number in Table 6 = the number of TPs in Table 1) Denominator is total number of Xpert tests performed (Total Xpert positive results from Table 1 first row): 2 – No
Did the study report any Xpert rifampicin resistant positive results in culture-negative specimens?	1 – Yes -> number reported: 2 – No

(Continued)

Did the study report nontuberculous mycobacteria (NTM)? Record number NTM over the number of cultures performed	1 – Yes -> number reported: 2 – No
If NTMs were identified, record number of Xpert positive results among NTMs	#Xpert positive tests among total number NTMs: 9 – Unknown/NR

Abbreviations: LJ: Löwenstein–Jensen; MGIT: Mycobacteria Growth Indicator Tube; NR: not reported; NTM: nontuberculous mycobacteria; PTB: pulmonary tuberculosis.

TABLES, examples

Table 1.

Tuberculosis**detection, all** participants		**Confirmed tuberculosis**		**Total**
		Yes	**No**	
Xpert Ultra result	Positive			
	Negative			
	Total			

Table 2.

Tuberculosis detection, smear positive		**Confirmed tuberculosis**		**Total**
		Yes	**No**	
Xpert Ultra result	Positive			
	Negative			
	Total			

Table 3.

Tuberculosis**detection, smear negative**		**Confirmed tuberculosis**		**Total**
		Yes	**No**	
Xpert Ultra	Positive			
	Negative			

(Continued)

	Total			

Table 4.

Tuberculosis**detection, 'trace' results**		**Confirmed tuberculosis**		**Total**
		Yes	**No**	
Xpert Ultra	Positive			
	Negative			
	Total			

Table 5.

Rifampicin resistance detection		**Rifampicin-resistant**		**Total**
		Yes	**No**	
Xpert Ultra	Positive			
	Negative			
	Total			

Appendix 3. Rules for QUADAS-2 and QUADAS-C

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 Ultra or Xpert MTB/RIF for pulmonary tuberculosis detection

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: Was a case-control design avoided? Studies using a case-control design were not included in the review because this study design, especially when used to compare results in severely ill patients with those in relatively healthy individuals, may lead to overestimation of accuracy in diagnostic studies. We answered ‘yes' for all studies.

Signalling question 3: Did the study avoid inappropriate exclusions? We answered ‘yes' if the study included both smear-positive and smear-negative individuals; ‘no' if the study included primarily or exclusively smear-positive or smear-negative patients; and ‘unclear' if we could not tell. We also answered ‘no' if the study included primarily or exclusively patients who had undergone previous treatment (retreatment patients).

In our 'Risk of bias' judgement, we also considered the condition of the specimen, and whether the study used fresh or frozen specimens.

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 routine practice. We answered 'low concern' if patients were evaluated in local hospitals or primary care centres. We answered 'high concern' if patients were evaluated exclusively as inpatients in tertiary care centres or if the setting did not match the review question, for example using the index for decisions about the need for airborne isolation. We answered 'unclear concern' if the clinical setting was not reported or information was insufficient to make a decision. We also answered 'unclear concern' if Xpert MTB/RIF or Xpert Ultra testing was done at a central-level laboratory, and the clinical setting was not reported for the following reason: it was difficult to tell if a given reference laboratory provided services mainly to very sick patients.

Xpert Ultra or Xpert MTB/RIF for rifampicin resistance detection

Domain 1: Patient selection is the same as for Xpert for pulmonary tuberculosis detection except for the following.

Signalling question 3: Did the study avoid inappropriate exclusions? We answered 'yes' if the study included both smear-positive and smear-negative individuals; 'no' if the study included primarily or exclusively smear-positive or smear-negative patients; and 'unclear' if we could not tell. We answered 'yes' if the study included primarily or exclusively retreatment patients because the group at risk for rifampicin resistance includes patients who had undergone previous treatment.

Domain 2: Index test

Xpert Ultra or Xpert MTB/RIF for pulmonary tuberculosis detection

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 judged '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 was true for most studies. We answered 'unclear concern' if the ratio of the Xpert Ultra or Xpert MTB/RIF sample reagent: specimen volume was not 2:1 for a raw specimen or 3:1 for a sediment, as recommended by the manufacturer. Central-level laboratories use more highly trained staff than peripheral and intermediate-level laboratories. However, we did not consider this to be a concern about applicability because, in some studies, the reason the index test was performed in a central-level laboratory was the requirement for a sophisticated laboratory infrastructure to perform culture (reference standard) not to perform Xpert.

Xpert Ultra or Xpert MTB/RIF for rifampicin resistance detection

Domain 2: Index test is the same as for Xpert for pulmonary tuberculosis detection.

Domain 3: Reference standard

Xpert Ultra or Xpert MTB/RIF for pulmonary tuberculosis detection

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?

For the reference standard, all studies used culture, which is generally considered to be the best reference standard for tuberculosis. Two studies used a composite reference standard in addition to culture. We answered this signalling question 'yes' for all studies.

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

We answered 'yes' if the reference test provided an automated result (e.g. MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We answered 'no' if the study stated that the reference standard result was interpreted with knowledge of the index 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 the included studies did not speciate mycobacteria isolated in culture; 'low concern' if speciation was performed; and 'unclear concern' if we could not tell.

Xpert Ultra or Xpert MTB/RIF for rifampicin resistance detection

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 or a line probe assay such as MTBDR*plus* was used. These were 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 (e.g. 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 Ultra or Xpert MTB/RIF 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 judged applicability to be of 'low concern' for those studies evaluating Xpert for rifampicin resistance because these specimens had already been identified as *Mycobacterium tuberculosis* positive.

Domain 4: Flow and timing

Xpert Ultra or Xpert MTB/RIF for 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? We expected that in most included studies specimens for Xpert MTB/RIF or Xpert Ultra and culture would be obtained at the same time, when patients were evaluated for presumptive pulmonary tuberculosis. However, even if there was 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; or '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. We acknowledge that it is possible that some specimens could undergo solid culture and others liquid culture, which could potentially result in variations in accuracy; however, 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 Ultra or Xpert MTB/RIF for rifampicin resistance detection

Domain 4: Flow and timing is the same as for Xpert Ultra or Xpert MTB/RIF for pulmonary tuberculosis detection.

Judgements for 'Risk of bias' assessments for a given domain are as follows.

- 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 further discussed 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 further discussed the 'Risk of bias' judgement for the domain.

Comparative accuracy (QUADAS-C): Xpert Ultra versus Xpert MTB/RIF

Comparative study design: Which of the following study designs does the primary study most strongly resemble?

Paired

Randomized

Other, specify

Comparison of index tests: Describe how patients were selected to undergo each of the index tests in the comparison. If randomization was used to assign individual patients (or clusters of patients) to index tests, describe the randomization process. Add flow diagram if available.

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Xpert Ultra**	**Xpert MTB/RIF**
Signalling questions	1 Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Yes/No/Unclear
	2 Was a case-control design avoided?	Yes/No/Unclear	Yes/No/Unclear
	3 Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	Could the selection of patients have introduced bias?	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	Are there concerns that the included patients do not match the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Xpert Ultra vs Xpert MTB/RIF**	
Signalling questions	1 Was risk of bias for this domain judged 'low' for all index tests?	Yes/No/Unclear	
	2 Was the intention for patients *either* to receive all index tests or to be randomly allocated to index tests?	Yes/No/Unclear	
	3 If patients were randomized, was the allocation sequence random?	Yes/No/Unclear/Not applicable	
	4 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Yes/No/Unclear/Not applicable	
	5 Were separate, sputum specimens tested with both tests or split raw sputum allocated and tested at random?	Yes/No/Unclear Not applicable	
Risk of bias	Could the selection of patients have introduced bias in the comparison?	Low/High/Unclear	
Domain: Index tests			
Single test accuracy (QUADAS-2)		**Xpert Ultra**	**Xpert MTB/RIF**
Signalling questions	1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear	Yes/No/Unclear
	2 If a threshold was used, was it prespecified?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low/High/Unclear	Low/High/Unclear

(Continued)

Concerns regarding applicability	Are there concerns that the index test, its conduct, or its interpretation differs from the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Xpert Ultra vs Xpert MTB/RIF**	
Signalling questions	1 Was risk of bias for this domain judged 'low' for all index tests?	Yes/No/Unclear	
	2 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Yes/No/Unclear/Not applicable	
	3 If patients received multiple index tests, is undergoing one index test *unlikely* to affect the performance of the other index test(s)?	Yes/No/Unclear/Not applicable	
	4 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes/No/Unclear	
Risk of bias	Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Low/High/Unclear	
Domain: Reference standard			
Single test accuracy (QUADAS-2)		**Xpert Ultra**	**Xpert MTB/RIF**
Signalling questions	1 Is the reference standard likely to correctly classify the target condition?	Yes/No/Unclear	Yes/No/Unclear
	2 Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Xpert Ultra vs Xpert MTB/RIF**	
Signalling questions	1 Was risk of bias for this domain judged 'low' for all index tests?	Yes/No/Unclear	
	2 Did the reference standard avoid incorporating any of the index tests?	Yes/No/Unclear	
Risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?	Low/High/Unclear	
Domain: Flow and timing			

(Continued)

Single test accuracy (QUADAS-2)		**Xpert Ultra**	**Xpert MTB/RIF**
Signalling questions	1 Was there an appropriate interval between index tests and reference standard?	Yes/No/Unclear	Yes/No/Unclear
	2 Did all patients receive the same reference standard?	Yes/No/Unclear	Yes/No/Unclear
	Were all patients included in the analysis?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	Could the patient flow have introduced bias?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Xpert Ultra vs Xpert MTB/RIF**	
Signalling questions	1 Was risk of bias for this domain judged 'low' for all index tests?	Yes/No/Unclear	
	2 Was there an appropriate interval between the index tests?	Yes/No/Unclear	
	3 Was the same reference standard used for all index tests?	Yes/No/Unclear	
	4 Are the proportions and reasons for missing data similar across index tests?	Yes/No/Unclear	
Risk of bias	Could the patient flow have introduced bias in the comparison?	Low/High/Unclear	

Appendix 4. Statistical appendix

Bayesian bivariate hierarchical model

The Bayesian bivariate hierarchical model used for the meta-analyses is summarized below. The hierarchical framework took into account heterogeneity between studies and also between centres within two of the largest studies. The model was derived as an extension of previously described models (Chu 2009; Reitsma 2005). An OpenBUGS program to fit this model is provided below. Three independent, dispersed sets of starting values were used to run separate chains. The Gelman-Rubin statistic within the OpenBUGS program was used to assess convergence. No convergence problems were observed. The first 10,000 iterations were treated as burn-in iterations and dropped. Summary statistics were obtained based on a total of 150,000 iterations resulting from the three separate chains.

Notation: From the jth centre in the ith study we extracted the cross-tabulation between the index and reference tests TPij, FPij, TNij, FNij. The sensitivity in ijth study is denoted by Sij and the specificity by SPij. We denote the Binomial probability distribution with sample size N and probability p as Binomial(p,N), the Bivariate Normal probability distribution with mean vector μ and variance-covariance matrix Σ as BVN(μ, Σ), the univariate Normal distribution with mean m and variance s by N(m, s) and the Uniform probability distribution between a and b by Uniform(a,b).

Likelihood Figure 13

Figure 13. Bayesian bivariate hierarchical model, likelihood.

Centre-level:

For studies with only 1 centre:

$$TP_{i1} \sim Binomial(S_i, TP_{i1} + FN_{i1}), TN_{i1} \sim Binomial(SP_i, TN_{i1} + FP_{i1})$$

For multicentre studies:

$$TP_{ij} \sim Binomial(S_{ij}, TP_{ij} + FN_{ij}), TN_{ij} \sim Binomial(SP_{ij}, TN_{ij} + FP_{ij})$$

$$\begin{pmatrix} logit(S_{ij}) \\ logit(SP_{ij}) \end{pmatrix} \sim BVN(l_i, \Sigma_i),$$

where $l_i = \begin{pmatrix} logit(S_i) \\ logit(SP_i) \end{pmatrix}$ and $\Sigma_i = \begin{pmatrix} \sigma_{i1}^2 & k_i\sigma_{i1}\sigma_{i2} \\ k_i\sigma_{i1}\sigma_{i2} & \sigma_{i2}^2 \end{pmatrix}$

Study-level:

$$\begin{pmatrix} logit(S_i) \\ logit(SP_i) \end{pmatrix} \sim BVN\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, T = \begin{pmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ \rho\tau_1\tau_2 & \tau_2^2 \end{pmatrix}\right)$$

The pooled sensitivity is given by 1/1+exp ($-\mu_1$) and pooled specificity as 1/1+exp (μ_2).

Prior distributions Figure 14.

Figure 14. Bayesian bivariate hierarchical model, prior distributions.

$$\mu_1 \text{ and } \mu_2 \sim N(0, 100)$$

$$k_i \text{ and } \rho \sim U(-1,1)$$

$$\frac{1}{\sigma_1^2}, \frac{1}{\sigma_2^2}, \frac{1}{\tau_1^2} \text{ and } \frac{1}{\tau_2^2} \sim Gamma(\text{shape}=2, \text{rate}=0.5)$$

Prior distributions were placed over the coefficients in the linear function: a1 and a2~ N(0,4) and b1 and b2~ N(0,1.39) (Buzoianu 2008).

```
# BIVARIATE MODEL ASSUMING PERFECT CULTURE REFERENCE TEST
model {
for(i in 1:6) {
############################## LIKELIHOOD
logit(TPR[i]) <- l[i,1]
logit(FPR[i]) <- -l[i,2]
pos[i]<-TP[i]+FN[i]
neg[i]<-TN[i]+FP[i]
TP[i] ~ dbin(TPR[i],pos[i])
FP[i] ~ dbin(FPR[i],neg[i])
se[i] <- TPR[i]
sp[i] <- 1-FPR[i]
l[i,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])
}
############################## HYPER PRIOR DISTRIBUTIONS
mu[1] ~ dnomr(0.0.25) # replaced by mu[1] ~ dnorm(0,0.01) in sensitivity analysis to check impact of less informative prior
mu[2] ~ dnomr(0.0.25) # replaced by mu[2] ~ dnorm(0,0.01) in sensitivity analysis to check impact of less informative prior
T[1:2,1:2]<-inverse(TAU[1:2,1:2])
#### BETWEEN-STUDY VARIANCE-COVARIANCE MATRIX
TAU[1,1] <- tau[1]*tau[1]
TAU[2,2] <- tau[2]*tau[2]
TAU[1,2] <- rho*tau[1]*tau[2]
TAU[2,1] <- rho*tau[1]*tau[2]
tau[1] <- pow(prec[1],-0.5) # replaced by tau[1] ~ dunif(0,3) in sensitivity analysis to check impact of less informative prior
tau[2] <- pow(prec[2],-0.5) # replaced by tau[2] ~ dunif(0,3) in sensitivity analysis to check impact of less informative prior
#### prec = between-study precision in the logit(sensitivity)and logit(specificity)
prec[1] ~ dgamma(2,0.5) # replaced by prec[1] <- powtau[1],-2) in sensitivity analysis to check impact of less informative prior
prec[2] ~ dgamma(2,0.5) # replaced by prec[2] <- powtau[2],-2) in sensitivity analysis to check impact of less informative prior
rho ~ dunif(-1,1)
############################## OTHER PARAMETERS OF INTEREST
#### POOLED SENSITIVITY AND SPECIFICITY
Pooled_S<-1/(1+exp(-mu[1]))
Pooled_C<-1/(1+exp(-mu[2]))
} #### END OF PROGRAM
#################################################################################

############################## DATA ###################################
#################################################################################
TP[] FP[] FN[] TN[]
```

50 8 6 173
175 1 25 76
408 43 54 934
62 18 10 149
45 5 2 144

23 10 0 147
116 3 7 140
END
row 1 Berhanu 2018
row 2 Chakravorty 2017
row 3 Dorman 2018
row 4 Mishra 2019a
row 5 Opota 2019

row 6 Pereira 2020
row 7 Piersimoni 2019

Appendix 5. Bayesian bivariate hierarchical model

Figure 13 Bayesian bivariate hierarchical model, likelihood

Figure 14 Bayesian bivariate hierarchical model, prior distributions

Appendix 6. QUADAS-C judgements, pulmonary tuberculosis

Figure 15

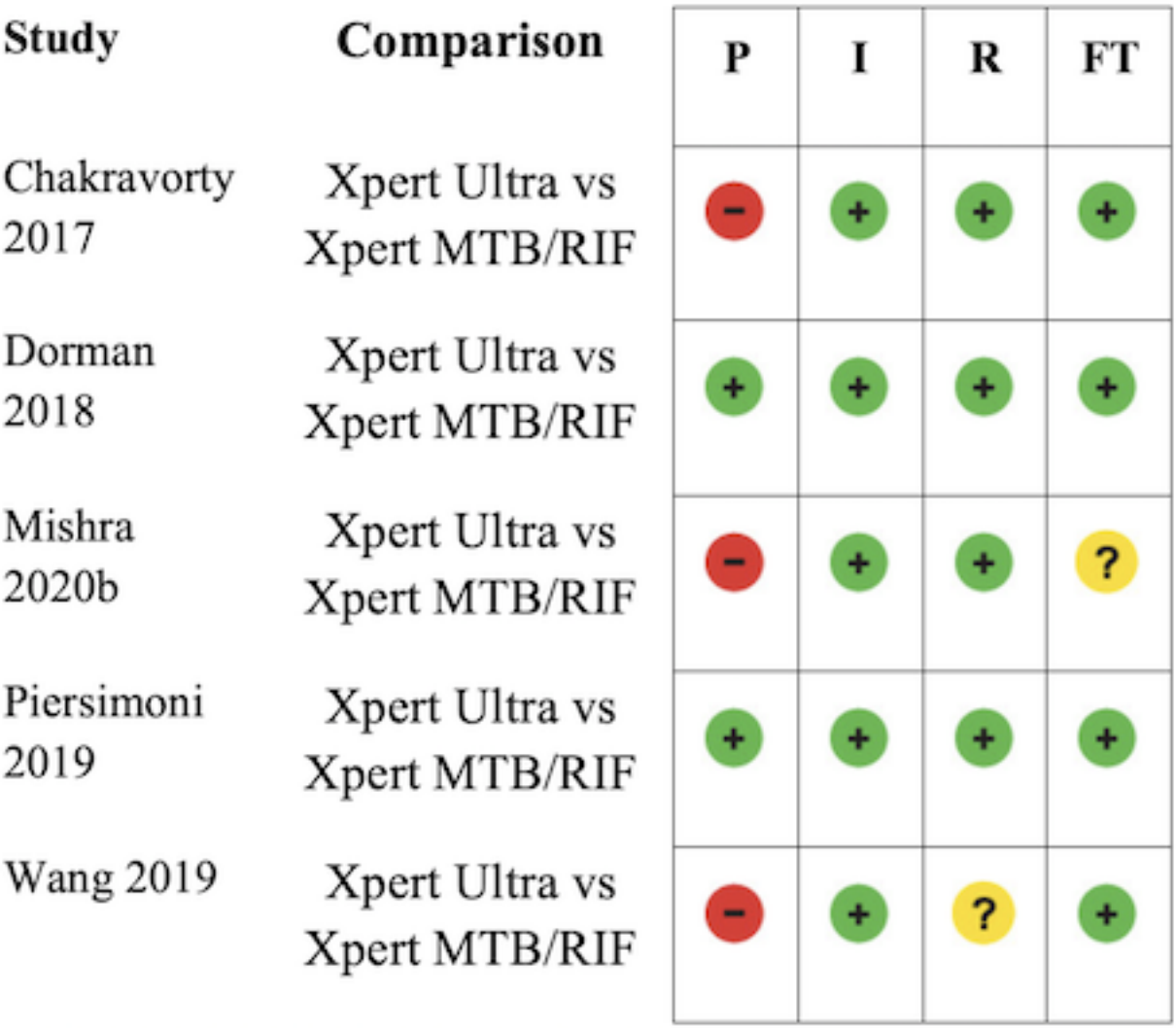
Figure 15. Table. Risk of bias concerns summary for detection of pulmonary tuberculosis: review authors' judgements about each domain for each included study, QUADAS-C judgements. P: Patient selection, I: Index test, R: Reference standard, FT: Flow and Timing

Study	Comparison	P	I	R	FT
Berhanu 2018	Xpert Ultra vs Xpert MTB/RIF	+	+	+	+
Chakravorty 2017	Xpert Ultra vs Xpert MTB/RIF	−	+	+	+
Dorman 2018	Xpert Ultra vs Xpert MTB/RIF	+	+	+	+
Mishra 2020a	Xpert Ultra vs Xpert MTB/RIF	+	+	+	+
Mishra 2020b	Xpert Ultra vs Xpert MTB/RIF	−	+	+	+
Opota 2019	Xpert Ultra vs Xpert MTB/RIF	+	+	+	+
Pereira 2020	Xpert Ultra vs Xpert MTB/RIF	+	+	?	+
Piersimoni 2019	Xpert Ultra vs Xpert MTB/RIF	+	+	+	+
Wang 2019	Xpert Ultra vs Xpert MTB/RIF	−	+	?	+

Appendix 7. QUADAS-C judgements, rifampicin resistance

Figure 16

Figure 16. Table. Risk of bias concerns summary for detection of rifampicin resistance: review authors' judgements about each domain for each included study, QUADAS-C judgements. P: Patient selection, I: Index test, R: Reference standard, FT: Flow and Timing



FEEDBACK

Boyles, October 2014

Summary

Name: Tom Boyles

Affiliation: University of Cape Town

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

In the initial version of Steingart et al's systematic review of the Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Steingart 2013) includes 15 studies where Xpert MTB/RIF was used as an initial test replacing smear microscopy, with the majority of patients being drawn from two major studies (Boehme 2010, Boehme 2011). My comment relates to the appropriate reference standard

for tuberculosis is these studies. The systematic review appraised the quality of included studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting 2011) tool which states that estimates of test accuracy are based on the assumption that the reference standard is 100% sensitive and that specific disagreements between the reference standard and index test result from incorrect classification by the index test.

For each of the studies in question the reference standard for tuberculosis is listed as "Löwenstein-Jensen culture and MGIT 960" and the review considers that the reference standard is likely to correctly classify the target condition. There is considered to be low risk of bias or applicability concerns relating to the reference test.

However, in Boehme et al 2010 there were 105 patients with 'clinical tuberculosis' who were excluded from the analysis. These patients were negative by the reference standard of Löwenstein-Jensen culture and MGIT 960 and should have been included in the 'no tuberculosis' group. In Boehme et al 2011 there were 153 similar patients who were excluded from the analysis.

Neither paper gives justification for the exclusion of these patients who according to QUADAS-2 were negative by the reference standard and should be included in the 'no tuberculosis' group. Ideally the systematic review should be amended to include these patients but if the data is unavailable the risk of bias should be acknowledged.

Note from the Editors: In addition to the above feedback, Boyles et al. published a case study in The International Journal of Tuberculosis and Lung Disease which outlined the above arguments, and illustrates this with a case study (Boyles 2014 *); which the Cochrane authors respond to, in the same journal (see below).*

Reply

The review authors thank Boyles et al. for this comment. They raise important points about the selective exclusion of culture negative clinical tuberculosis cases in the Boehme studies.

We considered the published case study (Boyles 2014) in detail, and in response we carried out additional analyses to determine whether the Boehme studies unduly influenced the overall findings of this Cochrane review. One way we did this was by repeating the meta-analysis with studies for which we could extract data for all enrolled participants, including patients classified as 'clinical tuberculosis' with negative sputum culture. We considered these participants as not having tuberculosis. In the new analysis, we found pooled sensitivity and specificity estimates to be similar to those we previously reported.

We published our findings as a response to Boyles et al. in *The International Journal of Tuberculosis and Lung Disease* (Steingart 2015).

In the updated Cochrane Review, for Boehme 2010, we included culture negative results (clinical tuberculosis cases) in determinations of Xpert MTB/RIF specificity. For Boehme 2011, we did not have data for clinical tuberculosis, and therefore, in the flow and timing domain, we changed our judgement for risk of bias to 'high'.

WHAT'S NEW

Date	Event	Description
17 February 2021	New citation required and conclusions have changed	To extend the work of our previous Cochane Review (Horne 2019), we performed this review update to inform updates to WHO policy.
17 February 2021	New search has been performed	We updated the literature search to 28 January 2020. Prespecifed changes to the protocol for this review update are given in Table 8.

HISTORY

Protocol first published: Issue 1, 2012
Review first published: Issue 1, 2013

Date	Event	Description
5 June 2019	New citation required but conclusions have not changed	The findings in this update are consistent with those reported previously (Steingart 2014).
5 June 2019	New search has been performed	We identified 95 unique studies, integrating 77 new studies since publication of the Cochrane Review (Steingart 2014).
30 June 2015	Amended	See Steingart 2014 for these amendments. Added revised data including (smear-positive culture negatives) for Boehme 2010 and Rachow 2011. Added corrected data for Hanrahan 2013. Added test and analysis for history of tuberculosis (TB). Amended patient selection for Boehme 2011 to high risk of bias.
16 March 2015	Feedback has been incorporated	Feedback from Dr Tom Boyles at University of Cape Town has been incorporated and responded to.
6 May 2014	Amended	See Steingart 2014 for this amendment. Following information obtained from a trial author, details of the version of Xpert MTB/RIF used in Balcells 2012 have been corrected.
13 February 2014	Amended	Sentence moved in Abstract; corrected "pooled median sensitivity" to "median pooled sensitivity" throughout.
30 November 2013	New citation required but conclusions have not changed	We conducted a new search and revised the review as described.
30 November 2013	New search has been performed	1. We performed an updated literature search on 7 February 2013. 2. For smear microscopy as a comparator test, we added a descriptive plot showing the estimates of sensitivity and specificity of Xpert compared with those of smear microscopy in studies that reported on both tests. 3. We included studies using Xpert version G4 (two studies) and studies evaluating Xpert in primary care clinics (two studies). These studies did not change the overall findings. 4. We improved the QUADAS-2 assessment concerning applicability. 5. For TB detection, we repeated our earlier meta-regression analyses within subgroups defined by smear status. 6. For rifampicin resistance detection, we performed univariate meta-analyses for sensitivity and specificity separately in order to include studies in which no rifampicin resistance was detected. We also performed a sensitivity analysis using the bivariate random-effects model for the subset of studies that provided data for both sensitivity and specificity. 7. We revised the 'Summary of findings' table to include clinical scenarios with prevalence levels recommended by the World Health Organization. 8. In the Background, we shortened the section on alternative tests to include only those tests most relevant to the review. 9. We added health economic considerations to the Discussion. 10. We added updated TB surveillance information.
17 January 2013	Amended	We made minor edits to the text to correct typographical errors. In addition, we replaced Figures 6, 8, 11, and 13 with new figures with minor modifications to the prediction regions.

CONTRIBUTIONS OF AUTHORS

MP conceived the original idea for the review.
KRS, MP, and ND wrote the original protocol (Sohn 2012).

For this review update:
Vittoria Lutje designed the search strategy.
JSZ, JSK, MK, KRS, and DJH assessed articles for inclusion and extracted data.
JSZ and MK managed the database.
JSZ, IS, ND, KRS, and DJH analysed the data and interpreted the analyses.
JSZ, JSK, IS, MK, ND, KRS, and DJH drafted the manuscript. In particular, IS and ND drafted the statistical analysis section and the statistical appendix. EAO and FH drafted the section on patient health outcomes in the Discussion. AAZ drafted the section on economic analyses in the Discussion.
SGS and MP provided critical comments to the manuscript.
All authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

JSZ received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

JSK has no known conflicts of interest.

IS received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

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

ND has no known conflicts of interest.

SGS is employed by the Foundation for Innovative New Diagnostics (FIND). FIND has conducted studies and published on Xpert MTB/RIF as part of a collaborative project between FIND, a Swiss nonprofit; Cepheid, a US company; and academic partners. The product developed through this partnership was developed under a contract that obligated FIND to pay for development costs and trial costs and Cepheid to make the test available at specified preferential pricing to the public sector in low- and middle-income countries. In addition, FIND conducted studies for the Xpert MTB/RIF Ultra assay, which have also been published.

EAO received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

FH received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

AAZ received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

MP serves on the Scientific Advisory Committee of Foundation for Innovative New Diagnostics (FIND), Geneva. FIND is a nonprofit agency that works on global health diagnostics.

KRS received funding from USAID, administered by the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland. In addition, she has received financial support from Cochrane Infectious Diseases, UK; McGill University, Canada; and the World Health Organization Global Tuberculosis Programme, Switzerland, for the preparation of related 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.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Table 8 describes prespecified changes for this review update. We performed the review as a comparative review and changed the title to 'Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis'. In addition, we restated the objective as: to compare the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for detection of pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis.

We clarified types of studies: we included cross-sectional and cohort type diagnostic accuracy studies that directly compared the index tests in participants with presumptive pulmonary tuberculosis. These study designs included paired and randomized comparative accuracy studies. Paired comparative accuracy studies are those in which each participant receives both index tests. Randomized comparative accuracy studies are those which randomly allocate participants to index tests, with each participant receiving only one index test.

In the protocol, we stated that we would extract data on industry sponsorship. As both Xpert Ultra and Xpert MTB/RIF are available at a concessional price for researchers in resource-limited settings, and are well-established tests, especially Xpert MTB/RIF, industry donation is rarely pursued, thus we did not consider that the additional analysis would have added value. We acknowledge that, in addition to funding, there are other reasons for conflicts of interest; however, we did not have time to pursue these. We are aware of a new tool being developed for this purpose: TACIT (Tool for Addressing Conflicts of Interest in Trials, tacit.one). We plan to avail ourselves of this new tool in updates of this review.

We summarized the frequency of Xpert Ultra trace-positive results, as well as the frequency of trace results in individuals with a history of tuberculosis.

We used QUADAS-2 and QUADAS-C to assess risk of bias in the included studies.

We planned to estimate the predicted sensitivity and specificity in a future study together with their 95% CrIs. Instead, we determined predictive values, which we thought would be more useful clinically.

We planned to perform a sensitivity analysis for studies that accounted for all participants in the analysis; however, for the detection of pulmonary tuberculosis, this criterion was satisfied by all studies.

We did not perform sensitivity analyses for Xpert MTB/RIF, as we performed these analyses in the previous Cochrane Review update, with most of these analyses including greater than 50 studies (Horne 2019). These sensitivity analyses did not change Xpert MTB/RIF performance.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotics, Antitubercular [pharmacology]; *Drug Resistance, Bacterial; Microbial Sensitivity Tests; *Mycobacterium tuberculosis [drug effects]; *Rifampin [pharmacology]; Sensitivity and Specificity; *Tuberculosis, Pulmonary [drug therapy]

MeSH check words

Humans