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[Diagnostic Test Accuracy Review]

Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children

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ABSTRACT

Background

Every year, at least one million children become ill with tuberculosis and around 200,000 children die. Xpert MTB/RIF and Xpert Ultra are World Health Organization (WHO)-recommended rapid molecular tests that simultaneously detect tuberculosis and rifampicin resistance in adults and children with signs and symptoms of tuberculosis, at lower health system levels. To inform updated WHO guidelines on molecular assays, we performed a systematic review on the diagnostic accuracy of these tests in children presumed to have active tuberculosis.

Objectives

Primary objectives

• To determine the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for (a) pulmonary tuberculosis in children presumed to have tuberculosis; (b) tuberculous meningitis in children presumed to have tuberculosis; (c) lymph node tuberculosis in children presumed to have tuberculosis; and (d) rifampicin resistance in children presumed to have tuberculosis

- For tuberculosis detection, index tests were used as the initial test, replacing standard practice (i.e. smear microscopy or culture)

- For detection of rifampicin resistance, index tests replaced culture-based drug susceptibility testing as the initial test

Secondary objectives

• To compare the accuracy of Xpert MTB/RIF and Xpert Ultra for each of the four target conditions

• To investigate potential sources of heterogeneity in accuracy estimates

- For tuberculosis detection, we considered age, disease severity, smear-test status, HIV status, clinical setting, specimen type, high tuberculosis burden, and high tuberculosis/HIV burden

- For detection of rifampicin resistance, we considered multi-drug-resistant tuberculosis burden

• To compare multiple Xpert MTB/RIF or Xpert Ultra results (repeated testing) with the initial Xpert MTB/RIF or Xpert Ultra result

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, Embase, Science Citation Index, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and the International Standard Randomized Controlled Trials Number (ISRCTN) Registry up to 29 April 2019, without language restrictions.

Selection criteria

Randomized trials, cross-sectional trials, and cohort studies evaluating Xpert MTB/RIF or Xpert Ultra in HIV-positive and HIV-negative children younger than 15 years. Reference standards comprised culture or a composite reference standard for tuberculosis and drug susceptibility testing or MTBDR*plus* (molecular assay for detection of *Mycobacterium tuberculosis* and drug resistance) for rifampicin resistance. We included studies evaluating sputum, gastric aspirate, stool, nasopharyngeal or bronchial lavage specimens (pulmonary tuberculosis), cerebrospinal fluid (tuberculous meningitis), fine needle aspirates, or surgical biopsy tissue (lymph node tuberculosis).

Data collection and analysis

Two review authors independently extracted data and assessed study quality using the Quality Assessment of Studies of Diagnostic Accuracy - Revised (QUADAS-2). For each target condition, we used the bivariate model to estimate pooled sensitivity and specificity with 95% confidence intervals (CIs). We stratified all analyses by type of reference standard. We assessed certainty of evidence using the GRADE approach.

Main results

For pulmonary tuberculosis, 299 data sets (68,544 participants) were available for analysis; for tuberculous meningitis, 10 data sets (423 participants) were available; for lymph node tuberculosis, 10 data sets (318 participants) were available; and for rifampicin resistance, 14 data sets (326 participants) were available. Thirty-nine studies (80%) took place in countries with high tuberculosis burden. Risk of bias was low except for the reference standard domain, for which risk of bias was unclear because many studies collected only one specimen for culture.

Detection of pulmonary tuberculosis

For sputum specimens, Xpert MTB/RIF pooled sensitivity (95% CI) and specificity (95% CI) verified by culture were 64.6% (55.3% to 72.9%) (23 studies, 493 participants; moderate-certainty evidence) and 99.0% (98.1% to 99.5%) (23 studies, 6119 participants; moderate-certainty evidence). For other specimen types (nasopharyngeal aspirate, 4 studies; gastric aspirate, 14 studies; stool, 11 studies), Xpert MTB/RIF pooled sensitivity ranged between 45.7% and 73.0%, and pooled specificity ranged between 98.1% and 99.6%.

For sputum specimens, Xpert Ultra pooled sensitivity (95% CI) and specificity (95% CI) verified by culture were 72.8% (64.7% to 79.6%) (3 studies, 136 participants; low-certainty evidence) and 97.5% (95.8% to 98.5%) (3 studies, 551 participants; high-certainty evidence). For nasopharyngeal specimens, Xpert Ultra sensitivity (95% CI) and specificity (95% CI) were 45.7% (28.9% to 63.3%) and 97.5% (93.7% to 99.3%) (1 study, 195 participants).

For all specimen types, Xpert MTB/RIF and Xpert Ultra sensitivity were lower against a composite reference standard than against culture.

Detection of tuberculous meningitis

For cerebrospinal fluid, Xpert MTB/RIF pooled sensitivity and specificity, verified by culture, were 54.0% (95% CI 27.8% to 78.2%) (6 studies, 28 participants; very low-certainty evidence) and 93.8% (95% CI 84.5% to 97.6%) (6 studies, 213 participants; low-certainty evidence).

Detection of lymph node tuberculosis

For lymph node aspirates or biopsies, Xpert MTB/RIF pooled sensitivity and specificity, verified by culture, were 90.4% (95% CI 55.7% to 98.6%) (6 studies, 68 participants; very low-certainty evidence) and 89.8% (95% CI 71.5% to 96.8%) (6 studies, 142 participants; low-certainty evidence).

Detection of rifampicin resistance

Xpert MTB/RIF pooled sensitivity and specificity were 90.0% (67.6% to 97.5%) (6 studies, 20 participants; low-certainty evidence) and 98.3% (87.7% to 99.8%) (6 studies, 203 participants; moderate-certainty evidence).

Authors' conclusions

We found Xpert MTB/RIF sensitivity to vary by specimen type, with gastric aspirate specimens having the highest sensitivity followed by sputum and stool, and nasopharyngeal specimens the lowest; specificity in all specimens was > 98%. Compared with Xpert MTB/RIF, Xpert Ultra sensitivity in sputum was higher and specificity slightly lower. Xpert MTB/RIF was accurate for detection of rifampicin resistance. Xpert MTB/RIF was sensitive for diagnosing lymph node tuberculosis. For children with presumed tuberculous meningitis, treatment decisions should be based on the entirety of clinical information and treatment should not be withheld based solely on an Xpert MTB/RIF result. The small numbers of studies and participants, particularly for Xpert Ultra, limits our confidence in the precision of these estimates.

PLAIN LANGUAGE SUMMARY

Xpert tests for active tuberculosis in children

Why is improving the diagnosis of pulmonary tuberculosis important?

In 2018, at least one million children became ill with tuberculosis and around 200,000 died. When detected early and effectively treated, tuberculosis is largely curable. Xpert MTB/RIF and Xpert Ultra are World Health Organization-recommended tests that simultaneously detect tuberculosis and rifampicin resistance in adults and children with tuberculosis symptoms. Rifampicin is an important anti-tuberculosis drug. Not recognizing tuberculosis early may result in delayed diagnosis and treatment, severe illness, and death. A false tuberculosis diagnosis may result in anxiety and unnecessary treatment.

What is the aim of this review?

To determine the accuracy of tests in symptomatic children for diagnosing pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance.

What was studied in this review?

Xpert MTB/RIF and Xpert Ultra, with results measured against culture and a composite reference standard (benchmarks), recognizing that neither reference is perfect in children.

What are the main results in this review?

A total of 49 studies were included. For pulmonary tuberculosis, we analysed 299 data sets including information describing nearly 70,000 children.

For a population of 1000 children:

Xpert MTB/RIF

- where 100 have pulmonary tuberculosis in sputum (by culture), 74 would be Xpert MTB/RIF-positive, of whom 9 (12%) would not have tuberculosis (false-positives); 926 would be Xpert MTB/RIF-negative; and 35 (4%) would have tuberculosis (false-negatives)

- where 100 have tuberculous meningitis (by culture), 86 would be Xpert MTB/RIF-positive, of whom 59 (69%) would not have tuberculosis (false-positives); 914 would be Xpert MTB/RIF-negative; and 23 (3%) would have tuberculosis (false-negatives)

- where 100 people have lymph node tuberculosis (by culture), 142 would be Xpert MTB/RIF-positive, of whom 97 (68%) would not have lymph node tuberculosis (false-positives); 858 would be Xpert MTB/RIF-negative; and 5 (1%) would have lymph node TB (false-negatives)

- where 100 have rifampicin resistance, 108 would have Xpert MTB/RIF-rifampicin resistance detected, of whom 18 (17%) would not have rifampicin resistance (false-positives); 892 would have Xpert MTB/RIF-rifampicin resistance NOT detected; and 10 (1%) would have rifampicin resistance (false-negatives)

Xpert Ultra

- where 100 have pulmonary tuberculosis in sputum (by culture), 100 would be Xpert Ultra-positive, of whom 27 (27%) would not have tuberculosis (false-positives); 900 would be Xpert Ultra-negative; and 27 (3%) would have tuberculosis (false-negatives)

How confident are we in the results of this review?

We are confident. We included many studies from different countries and settings and used two reference standards. Some studies included only children at referral centres or did not report the setting. Therefore, we could not assess how the tests would work in a primary care setting.

What children do the results of this review apply to?

Children with presumed pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, or rifampicin resistance.

What are the implications of this review?

The results of the review suggest Xpert tests have the potential to be used to detect tuberculosis and rifampicin resistance.

- The risk of missing a diagnosis of pulmonary tuberculosis confirmed by culture with Xpert MTB/RIF (in sputum) is low (4% of those whose Xpert MTB/RIF suggests they do not have tuberculosis) suggesting that only a small number of children with tuberculosis confirmed by culture will not receive treatment. The risk of wrongly diagnosing a child as having tuberculosis is slightly higher (12% of those whose Xpert MTB/RIF test suggests they do have tuberculosis). This may result in some of these children receiving unnecessary treatment.

- The risk of missing a diagnosis of rifampicin resistance with Xpert MTB/RIF is low (1% of those whose Xpert MTB/RIF suggests they do not have rifampicin resistance) suggesting that only a small number of children with tuberculosis will not receive the appropriate treatment. The risk of wrongly diagnosing a child as rifampicin resistance tuberculosis is higher (17% of those whose Xpert MTB/RIF test suggests they do have rifampicin resistance). This may result in some of these children receiving unnecessary treatment.

How up-to-date is this review?

To 29 April 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis in children

Review question: what is the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis in sputum in children with signs and symptoms of pulmonary tuberculosis?

Patients/population: children with presumed pulmonary tuberculosis

Index tests: Xpert MTB/RIF and Xpert Ultra

Role: an initial test

Threshold for index tests: an automated result is provided

Reference standard: culture

Types of studies: cross-sectional and cohort studies

Setting: primary care facilities and local hospitals

Index test	Effect (95% CI)	Number of participants (studies)	Test result	Number of results per 1000 patients tested(95% CI)			Certainty of the evidence (GRADE)
				Prevalence 1%	Prevalence 10%	Prevalence 20%	
Xpert MTB/RIF	Pooled sensitivity 0.65 (95% CI 0.55 to 0.73)	493 (23)	True-positives	6 (6 to 7)	65 (55 to 73)	129 (111 to 146)	⊕⊕⊕◯ **MODERATE** [a,b]
			False-negatives	4 (3 to 4)	35 (27 to 45)	71 (54 to 89)	
	Pooled specificity 0.99 (95% CI 0.98 to 0.99)	6119 (23)	True-negatives	980 (971 to 985)	891 (883 to 896)	792 (785 to 796)	⊕⊕⊕◯ **MODERATE** [c]
			False-positives	10 (5 to 19)	9 (4 to 17)	8 (4 to 15)	
Xpert Ultra	Pooled sensitivity 0.73 (95% CI 0.65 to 0.80)	136 (3)	True-positives	7 (6 to 8)	73 (65 to 80)	146 (129 to 159)	⊕⊕◯◯ **LOW** [d,e]
			False-negatives	3 (2 to 4)	27 (20 to 35)	54 (41 to 71)	
	Pooled specificity 0.97 (95% CI 0.96 to 0.98)	551 (3)	True-negatives	960 (950 to 970)	873 (864 to 882)	776 (768 to 784)	⊕⊕⊕⊕ **HIGH**
			False-positives	30 (20 to 40)	27 (18 to 36)	24 (16 to 32)	

CI: confidence interval.

Prevalence levels were suggested by the WHO Global Tuberculosis Programme.

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

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

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

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

[e]The number of children with pulmonary tuberculosis contributing to this analysis for observed sensitivity was low. We downgraded one level for imprecision.

GRADE certainty of the evidence.

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

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

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

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

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

Summary of findings 2. Xpert MTB/RIF for tuberculous meningitis in children

Review question: what is the diagnostic accuracy of Xpert MTB/RIF for tuberculous meningitis in CSF in children with signs and symptoms of tuberculous meningitis?

Patients/population: children with presumed tuberculous meningitis

Index tests: Xpert MTB/RIF

Role: an initial test

Threshold for index tests: an automated result is provided

Reference standard: culture

Types of studies: cross-sectional and cohort studies

Setting: inpatient

Pooled sensitivity: 0.54 (95% CI 0.28 to 0.78) | **Pooled specificity:** 0.94 (95% CI 0.84 to 0.98)

Test result	Number of results per 1000 patients tested (95% CI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 1%	Prevalence 5%	Prevalence 10%		
True-positives	5 (3 to 8)	27 (14 to 39)	54 (28 to 78)	28 (6)	⊕◯◯◯ **VERY LOW** [a,b,c,d]

False-negatives	5 (2 to 7)	23 (11 to 36)	46 (22 to 72)		
True-negatives	929 (837 to 966)	891 (803 to 927)	844 (761 to 878)	213 (6)	⨁⨁◯◯ **LOW** [e,f]
False-positives	61 (24 to 153)	59 (23 to 147)	56 (22 to 139)		

CI: confidence interval; CSF: cerebrospinal fluid.
Prevalence levels were suggested by the WHO Global Tuberculosis Programme.
[a]As assessed by QUADAS-2, three studies (50%) had low risk of bias and risk of bias was unclear for the remainder. We downgraded one level for risk of bias.
[b]For individual studies, sensitivity estimates ranged from 0% to 100%. We thought that differences in enrolment criteria (different populations targeted), disease severity, and setting could only in part explain heterogeneity. We downgraded one level for inconsistency.
[c]The setting was unclear or reflected a tertiary care inpatient setting in three studies (50%). However, this is reflective of where the target condition would typically be diagnosed; therefore we did not downgrade for indirectness.
[d]The number of children with tuberculous meningitis contributing to this analysis for observed sensitivity was low. We thought the 95% CI around false-negatives and true-positives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded one level for imprecision.
[e]The quality of the reference standard was unclear in three studies (50%). We downgraded one level for risk of bias.
[f]We thought the 95% CI around false-positives and true-negatives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded one level for imprecision.
GRADE certainty of the evidence.
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 3. Xpert MTB/RIF for lymph node tuberculosis in children

Review question: what is the diagnostic accuracy of Xpert MTB/RIF for lymph node tuberculosis in a lymph node specimen in children with signs and symptoms of lymph node tuberculosis?
Patients/population: children with presumed lymph node tuberculosis
Index tests: Xpert MTB/RIF
Role: an initial test
Threshold for index tests: an automated result is provided
Reference standard: culture
Types of studies: cross-sectional and cohort studies

Setting: inpatient

Pooled sensitivity: 0.90 (95% CI 0.56 to 0.99) | **Pooled specificity:** 0.90 (95% CI 0.71 to 0.97)

Test result	Number of results per 1000 patients tested (95% CI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 1% Typically seen in	Prevalence 5% Typically seen in	Prevalence 10% Typically seen in		
True-positives	9 (6 to 10)	45 (28 to 49)	90 (56 to 99)	68 (6)	⊕◯◯◯ **VERY LOW** a,b,c
False-negatives	1 (0 to 4)	5 (1 to 22)	10 (1 to 44)		
True-negatives	889 (708 to 958)	853 (679 to 920)	808 (644 to 871)	142 (6)	⊕⊕◯◯ **LOW** d,e,f
False-positives	101 (32 to 282)	97 (30 to 271)	92 (29 to 256)		

CI: confidence interval.
Prevalence levels were suggested by the WHO Global Tuberculosis Programme.
[a]As assessed by QUADAS-2, three studies (50%) had high risk of bias. We downgraded one level for risk of bias.
[b]Three studies (50%) had high or unclear concern about applicability because, in these studies, patients were enrolled from inpatient tertiary care settings, which could lead to enrolment of children with more advanced disease. We did not downgrade for indirectness, as a more specialized centre for the diagnosis of extrapulmonary tuberculosis in children is expected.
[c]The number of children with lymph node tuberculosis contributing to this analysis for observed sensitivity was low. We thought the 95% CI around false-negatives and true-positives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded two levels for imprecision.
[d]As assessed by QUADAS-2, all studies (100%) had unclear risk of bias relative to the quality of the reference standard. We downgraded one level for risk of bias.
[e]For individual studies, specificity estimates ranged from 50% to 100%. For most studies, specificity was ≥ 96%. We did not downgrade for inconsistency.
[f]We thought the 95% CI around false-positives and true-negatives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded one level for imprecision
GRADE certainty of the evidence.
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

Summary of findings 4. Xpert MTB/RIF for rifampicin resistance in children

Review question: what is the diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance in children with signs and symptoms of tuberculosis?

Patients/population: children with presumed tuberculosis

Index tests: Xpert MTB/RIF

Role: an initial test

Threshold for index tests: an automated result is provided

Reference standard: phenotypic culture-based drug susceptibility testing and MTBDR*plus*

Types of studies: cross-sectional and cohort studies

Setting: inpatient

Pooled sensitivity: 0.90 (95% CI 0.68 to 0.98) | **Pooled specificity:** 0.98 (95% CI 0.88 to 0.99)

Test result	Number of results per 1000 patients tested (95% CI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 2%	Prevalence 10%	Prevalence 15%		
True-positives	18 (14 to 20)	90 (68 to 98)	135 (102 to 147)	20 (6)	⊕⊕◯◯ **LOW** [a]
False-negatives	2 (0 to 6)	10 (2 to 32)	15 (3 to 48)		
True-negatives	960 (862 to 970)	882 (792 to 891)	833 (748 to 842)	203 (6)	⊕⊕⊕◯ **MODERATE** [b,c]
False-positives	20 (10 to 118)	18 (9 to 108)	17 (8 to 102)		

CI: confidence interval.
Prevalence levels were suggested by the WHO Global Tuberculosis Programme.
[a]The number of children with rifampicin resistance contributing to this analysis for observed sensitivity was low. We thought the 95% CI around false-negatives and true-positives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded two levels for imprecision.
[b]For individual studies, specificity estimates ranged from 67% in Saini 2018 to 100%. For most studies, specificity was ≥ 97%. We did not downgrade for inconsistency.
[c]We thought the 95% CI around false-positives and true-negatives would likely lead to different decisions, depending on which confidence limits are assumed. We downgraded one level for imprecision.
GRADE certainty of the evidence.
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to each summary test accuracy measure.

BACKGROUND

Tuberculosis is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS), causing an estimated 1.2 million deaths in 2018 (WHO Global TB Report 2019). Globally during that year, an estimated 10 million people developed tuberculosis disease, including around one million children younger than 14 years and 205,000 children who died of the disease (WHO Global TB Report 2019). Recent models that have been accepted and supported by the World Health Organization (WHO) suggest that there is substantial underreporting as well as under-diagnosis of tuberculosis in children. Furthermore, tuberculosis-associated deaths take a disproportionate toll among children: 253,000 deaths were estimated in 2016 in children younger than 15 years, accounting for 6.9% of the total deaths notified in that year; of these deaths, 80% occurred in children younger than five years of age (Dodd 2017; Jenkins 2017). Estimates suggest that most deaths among children occur in undiagnosed cases and represent a missed opportunity to start adequate treatment (Jenkins 2017).

Tuberculosis treatment for children follows the same principles as for adults, and the same drugs are used in most cases. The standard four-drug combination regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol given daily for a period of two months followed by isoniazid and rifampicin given daily for an additional four to six months is used for treatment of drug-susceptible tuberculosis - both pulmonary and extrapulmonary forms. Central nervous system tuberculosis is an exception in that treatment with isoniazid and rifampicin is extended to a total of 12 months. The recent introduction of paediatric fixed-dose combinations with optimised dosing and taste masking has improved the efficiency of treatment (Wademan 2019). Treatment of drug-resistant tuberculosis in children generally has better outcomes than in adults. Of note, in August 2018, the WHO released a rapid communication containing new recommendations for treatment of child tuberculosis, including the use of all-oral regimens (Furin 2019; WHO 2018).

The diagnosis of child tuberculosis relies on a mix of clinical, epidemiological, radiological, and laboratory information. Child tuberculosis is typically paucibacillary (tuberculosis disease caused by a smaller number of bacteria), and young children cannot voluntarily produce sputum specimens (Marais 2005; Theart 2005). Hence, even under ideal clinical and laboratory conditions, only 30% to 40% of child tuberculosis cases are microbiologically confirmed (Dunn 2016). The probability of microbiological confirmation is increased in children with more severe or advanced disease (Marais 2006c; Marais 2006d). However, the diagnostic gap is perpetuated because conventional smear microscopy, which is of little value in diagnosing child tuberculosis, remains the most used and most widely available tuberculosis diagnostic method in low- and middle-income countries. Further, the clinical skills and equipment needed for sputum induction and gastric aspiration are often not available in peripheral health clinics (Reid 2012). Tuberculosis culture methods have shown greater, yet highly variable, sensitivity in child tuberculosis (Chiang 2017; Frigati 2015); unfortunately, tuberculosis culture to support diagnosis is not widely available in high-burden settings.

Xpert MTB/RIF represents a promising diagnostic modality for child tuberculosis. Since 2010, the WHO has recommended the use of Xpert MTB/RIF as the preferred initial microbiological test for people thought to have multi-drug-resistant tuberculosis or HIV-associated tuberculosis (strong recommendation); this recommendation was extended to include children with presumed tuberculosis on the strength of evidence reported in adults (WHO 2011). In 2013 this guidance was updated with a recommendation specific to children, that is, that Xpert MTB/RIF should be used as the preferred initial diagnostic test for children thought to have multi-drug-resistant tuberculosis or HIV-associated tuberculosis (strong recommendation; very low-quality evidence) and as the initial diagnostic test for all children with presumptive tuberculosis (conditional recommendation acknowledging resource implications; very low-quality evidence) (WHO 2013). At present, the WHO supports the use of Xpert MTB/RIF for diagnosis of child tuberculosis in the following four scenarios.

- As the initial diagnostic test of choice, rather than conventional smear microscopy or culture (conditional recommendation acknowledging resource implications; very low-quality evidence - also called certainty of evidence).
- For diagnosis in children suspected of having drug-resistant tuberculosis or HIV-associated tuberculosis (strong recommendation; very low-quality evidence).
- As a replacement test for culture in specific non-respiratory specimens (lymph nodes and other tissues) for children presumed to have extrapulmonary tuberculosis (conditional recommendation; very low-quality evidence).
- As the preferred initial diagnostic in cerebrospinal fluid (CSF) for children suspected of having tuberculous meningitis (strong recommendation given the urgency of rapid diagnosis; very low-quality evidence) (WHO 2014a).

The WHO does not currently recommend Xpert MTB/RIF for use with other specimen types such as stool. Further, existing guidelines acknowledge that all current recommendations regarding use of Xpert MTB/RIF in children rely on “very low-certainty evidence” and are currently evolving with expansion of the use of Xpert MTB/RIF Ultra (Xpert Ultra) (WHO 2017).

A non-inferiority analysis of Xpert Ultra compared to Xpert MTB/RIF found that Xpert Ultra has higher sensitivity than Xpert MTB/RIF, particularly in smear-negative, culture-positive specimens and in specimens from HIV-positive patients. Xpert Ultra was also found to have accuracy that was at least as good as Xpert MTB/RIF for detection of rifampicin resistance. However, it was noted that Xpert Ultra may have reduced specificity in settings with high tuberculosis burden. Current WHO recommendations for the use of Xpert MTB/RIF now also apply to the use of Xpert Ultra as the initial diagnostic test for all adults and children with signs and symptoms of tuberculosis as well as to testing of selected extrapulmonary specimens (cerebrospinal fluid, lymph nodes, and tissue specimens). However, a negative test result does not exclude tuberculosis in children (WHO 2017). This systematic review estimated and compared the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for children presumed to have pulmonary tuberculosis or specific forms of extrapulmonary tuberculosis.

Target condition being diagnosed

Tuberculosis is an infectious disease caused by bacteria within the *Mycobacterium tuberculosis* complex, most commonly *Mycobacterium tuberculosis* (*M tuberculosis*). Typically

disseminated through the air, *M tuberculosis* predominantly affects the lungs, causing pulmonary tuberculosis, and less typically can cause disease in other organs of the body in extrapulmonary tuberculosis forms. Lymph node tuberculosis is the most common form of extrapulmonary tuberculosis in children, and tuberculous meningitis results in the highest morbidity and mortality. For this review, we limited evaluation of extrapulmonary tuberculosis to lymph node tuberculosis and tuberculous meningitis because other forms of extrapulmonary tuberculosis in children are less common, and because evidence evaluating Xpert (Xpert MTB/RIF and Xpert Ultra) as a diagnostic tool for other forms of extrapulmonary child tuberculosis is sparse.

The natural history of tuberculosis in children is distinct from that in adults due to more frequent progression to primary tuberculosis disease (Marais 2004). Children younger than five years are at particularly high risk of progression to tuberculous disease following infection, but the risk for older children and adolescents is also higher than in adults. Overall, it is estimated that 90% of tuberculous disease in young children occurs within one year of infection (Marais 2014). In addition to age, factors such as nutritional status, immune-compromising conditions (e.g. HIV infection), BCG (bacillus Calmette–Guérin) vaccination status, and genetic susceptibility contribute to children's risk of disease progression. Immediately following infection with *M tuberculosis* in a child, hematogenous spread (by way of the bloodstream) can occur. The period of highest risk for presentation with tuberculous meningitis and miliary tuberculosis is one to three months following primary infection. Children between six months and two years of age are at particularly high risk of these severe forms of tuberculous disease. Approximately 50% of children in this age range progress to tuberculous disease following infection, and 20% to 40% of those children will present with disseminated disease (Marais 2004; Marais 2014). Children younger than five years most commonly present with hilar lymph node forms of intrathoracic tuberculous disease. Older children and adolescents more commonly manifest adult-type disease, including pleural tuberculosis and upper lobe consolidations (Marais 2004).

Laboratory confirmation of child tuberculosis disease is challenging for two reasons. First, child tuberculosis most commonly represents as a primary disease process, without the formation of cavities (Marais 2006a). The number of acid-fast bacilli (the presence of acid-fast bacilli on a sputum smear or other specimen often indicates tuberculous disease) present in forms of primary tuberculosis such as hilar lymph node or bronchial tuberculosis is substantially lower than the number present in a pulmonary cavity. Consequently, child tuberculosis is often referred to as 'paucibacillary', and it is more difficult to obtain the organisms needed to confirm disease via conventional smear or culture (Dunn 2016). Second, most children younger than six years of age lack the ability to expectorate sputum and are unable to voluntarily produce good-quality specimens. Therefore, respiratory specimens are often obtained through sputum induction. As children swallow respiratory secretions, early-morning gastric aspiration is another well-established approach to specimen collection. In one study, the yield of three consecutive morning gastric aspirates was similar to the yield of one induced sputum specimen (Zar 2005). Nasopharyngeal aspiration for respiratory specimens is a less invasive mode of specimen collection (Zar 2012). Stool has also been studied as a child tuberculosis diagnostic specimen; although sensitivity has been lower than with traditional specimens, this specimen has great appeal because collection is non-invasive and requires no training (Nicol 2013). Because laboratory diagnostics for tuberculosis perform poorly in children, algorithms involving signs, symptoms, tuberculosis exposure, HIV status, laboratory tests, and radiographic findings are commonly used to make a clinical diagnosis of child tuberculosis. However, these algorithms have been shown to perform differently across settings, and their sensitivity and specificity may be site-specific (David 2017).

Index test(s)

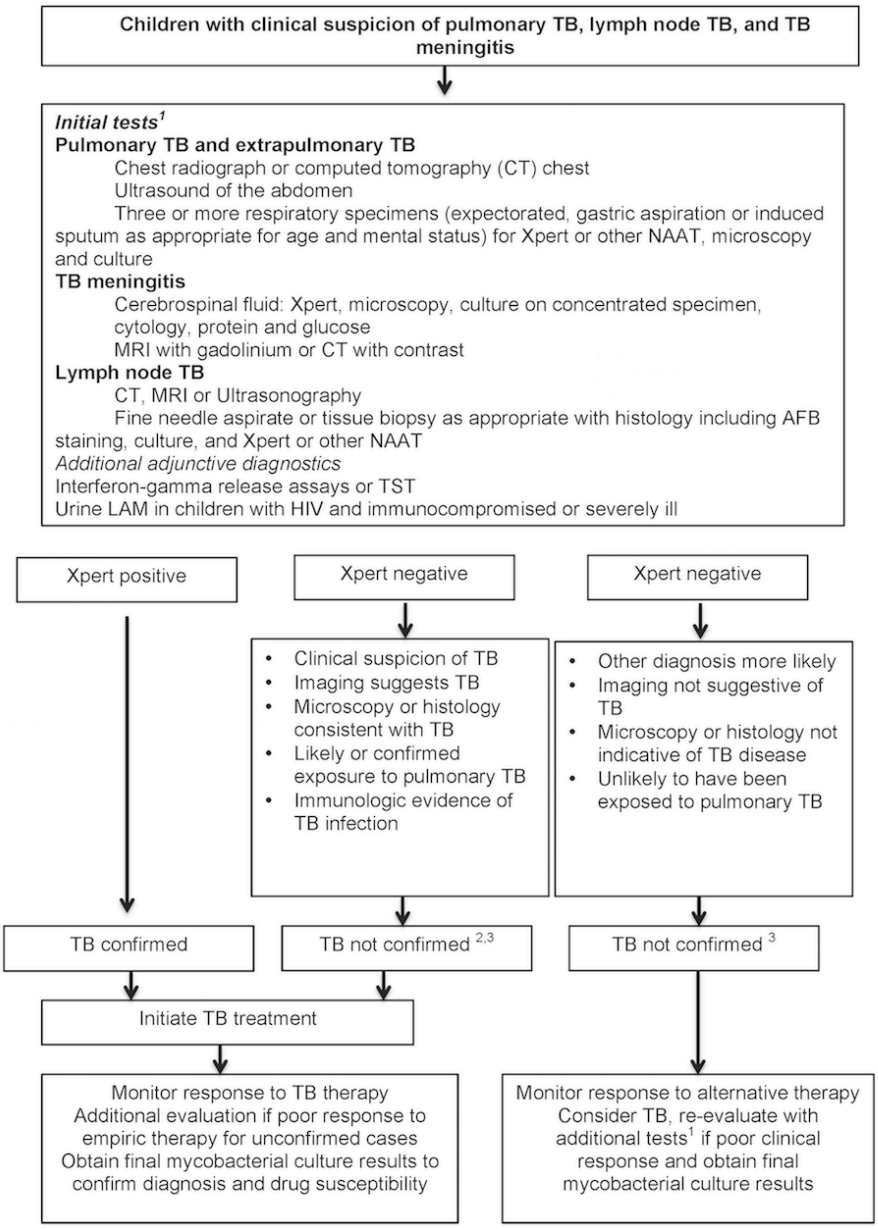
The index tests in this review are Xpert MTB/RIF and Xpert Ultra (Cepheid Inc, Sunnyvale, CA, USA). Xpert MTB/RIF and Xpert Ultra are nucleic acid amplification tests (NAATs) that function as an automated, closed system that performs real-time polymerase chain reaction (PCR). Specimens are processed using Xpert Sample Reagent and are incubated for 15 minutes, after which the processed samples are pipetted into the cartridge. These tests can be run by operators (such as laboratory technicians and nurses) with minimal technical expertise. Within two hours, the tests detect both live and dead *M tuberculosis* complex DNA and simultaneously recognize mutations in the *M tuberculosis* gene encoding the beta subunit of the RNA polymerase (*rpoB*) gene, which is the most common site of *M tuberculosis* mutations leading to rifampicin resistance. Xpert MTB/RIF and Xpert Ultra require an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules (WHO 2014b). The WHO has published extensive guidance and practical information on implementing the test (WHO 2014b).

There have been five generations of the cartridge: G1, G2, G3, G4, and Xpert Ultra. G1 to G4 cartridges initially improved the detection of tuberculosis and rifampicin resistance, but Xpert MTB/RIF sensitivity was still suboptimal in people with smear-negative (which is often seen in children) and HIV-associated tuberculosis. Xpert Ultra was developed in part to overcome this limitation and improve test sensitivity. There are limited data on the different sensitivity that Xpert Ultra offers as compared to the G4 cartridge; however, existing data suggest it may offer improved sensitivity for tuberculosis detection in hard-to-diagnose populations such as children, people living with HIV, and individuals with extrapulmonary tuberculosis (Dorman 2018; WHO 2017). To improve detection of *M tuberculosis*, Xpert Ultra incorporates two different multi-copy amplification targets (IS6110 and IS1081). These revisions resulted in an approximately 1–log improvement in the lower limit of detection compared with Xpert MTB/RIF, including improved differentiation of certain silent mutations, improved detection of rifampicin resistance in mixed infections, and avoidance of false-positive results for detection of rifampicin resistance in paucibacillary specimens (Chakravorty 2017). As mentioned above, Xpert Ultra also has decreased specificity compared to G4 and may be more likely to identify *M tuberculosis* DNA from prior episodes of tuberculosis disease, particularly in patients classified in the new 'trace' category (Dorman 2018). Trace call corresponds to the lowest bacillary burden for *M tuberculosis* detection, as described below (WHO 2017). This Cochrane Review includes studies that used any of the Xpert generations in the diagnosis of tuberculosis (pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis) in children younger than 15 years.

Clinical pathway

Figure 1 presents an example of the clinical pathway and placement of the index tests. A careful clinical history of tuberculosis exposure and symptoms is the first step in the diagnostic pathway for child tuberculosis. Children with household or other close and persistent exposure to a person with tuberculosis are at increased risk of tuberculosis infection and resultant progression to tuberculous disease. All children with recent exposure to tuberculosis must be evaluated for clinical symptoms and for examination findings consistent with tuberculous disease. Additional testing depends on the context but may include chest radiography and a test of tuberculosis infection. Symptoms of tuberculosis disease are generally persistent for longer than two weeks and are unremitting (Marais 2005). The most common symptoms are cough, fever, decreased appetite, weight loss or failure to thrive, and fatigue or reduced playfulness. Symptoms of extrapulmonary tuberculosis are typically localized, and diagnostic findings are generally obtained from the site of disease (Figure 1). However, no symptom-based diagnostic algorithms have been validated or have been shown to be reliable in multiple contexts. Symptom-based diagnostic algorithms tend to perform poorly in children younger than three years and in HIV-positive children - two populations at high risk for disease progression (Marais 2006b).

Figure 1. AFB: acid-fast bacilli; CT: computed tomography; LAM: mycobacterial lipoarabinomannan antigen; MRI: magnetic resonance imaging; NAAT: nucleic acid amplification test; TB: tuberculosis; TST: tuberculin skin test. The Clinical Pathway. Clinical suspicion of tuberculosis includes persistent cough, fever, weight loss or failure to thrive, lymphadenitis, irritability, lethargy, headache, vomiting or neurological symptoms, history of possible or confirmed exposure to *M tuberculosis*, increased risk for tuberculosis disease due to immunocompromising conditions.
[1]Availability of investigations and tests may be different in high- and low-resource settings and may influence the approach to the diagnosis of child tuberculosis.
[2]Non-microbiological confirmation of *M tuberculosis* does not exclude tuberculosis disease in children; therefore initiation of treatment should be considered empirically if other clinical indications are present.
[3]Mycobacterial culture results are rarely timely to aid the decision to initiate treatment but can confirm or refute clinical decision-making if positive.



Unfortunately, no clinical examination features are specific to pulmonary tuberculosis in children. However, examination findings in extrapulmonary tuberculosis can be quite specific when identified. Clinicians should consider medical comorbidities that increase the risk for tuberculous disease and should modify diagnostic algorithms accordingly. HIV infection not only significantly increases risk of tuberculosis in the paediatric population, it also raises the risk of increased disease severity. HIV-positive children, especially before effective antiretroviral therapy is established, often present with advanced tuberculosis such as disseminated disease and have high levels of immunosuppression, further complicating diagnosis and management.

Additional diagnostic imaging studies can assist in the diagnosis of pulmonary tuberculosis and nearly all forms of extrapulmonary tuberculosis. Tests of tuberculous infection, such as interferon gamma release assays or tuberculin skin tests, can also aid in establishing the probability of tuberculosis in a child but are not necessary to make the diagnosis. Diagnostic recommendations strongly suggest collecting appropriate specimens from suspected sites of involvement in both pulmonary and extrapulmonary tuberculosis for microbiological examination. The preferred specimen in pulmonary tuberculosis is sputum; however in young children who cannot expectorate, the specimen is commonly obtained via a gastric aspirate or induced sputum, and stool is increasingly used. To diagnose extrapulmonary tuberculosis, collection of samples targets the affected site of disease.

The purpose of Xpert MTB/RIF and Xpert Ultra testing is diagnosis of pulmonary and extrapulmonary tuberculosis and detection of rifampicin resistance. Results of Xpert can be used as a decision-making tool in the following ways.

- *M tuberculosis* detected/rifampicin resistance not detected: child would start treatment for drug-sensitive tuberculosis.
- *M tuberculosis* detected/rifampicin resistance detected: child would need further resistance testing and would start treatment for drug-resistant tuberculosis according to country guidelines.
- *M tuberculosis* not detected: a negative Xpert result does not rule out tuberculous disease; therefore, clinicians should still consider initiation of tuberculosis treatment in children with history and clinical or radiological features suggestive of tuberculosis disease despite a negative Xpert result. A negative Xpert result may also represent a true-negative.

Possible consequences of a false-positive and a false-negative result may include the following.

- False-positives (FPs): children and their families would likely experience anxiety and morbidity caused by additional testing, unnecessary treatment, and possible adverse effects; as well as missed time at school, possible stigma associated with tuberculosis or a diagnosis of drug-resistant tuberculosis, and the chance that a false-positive may halt further diagnostic evaluation for other causes of illness. Families also experience unnecessary expense.
- False-negatives (FNs): would imply increased risk of morbidity and mortality and delayed start of treatment.

Alternative test(s)

Alternative approaches to Xpert for diagnosis of tuberculosis are still used extensively globally. Main tests include examination of smears for acid-fast bacilli (tuberculosis bacteria) under a microscope (light microscopy, using the classical Ziehl-Neelsen staining technique), fluorescence microscopy, and light-emitting diode (LED)-based fluorescence microscopy. The sensitivity of smear microscopy ranges from 0% to 10% in children (Kunkel 2016). Examination of histology specimens under a microscope following a tissue biopsy targets finding acid-fast bacilli and granulomatous inflammation, frequently with caseous necrosis (necrotizing granulomas); however these options are seldom pursued to diagnose child tuberculosis in low-resource settings due to the invasive nature of the procedures and the technical expertise required. Lipoarabinomannan (LAM) antigen is a lipopolysaccharide present in the mycobacterial cell wall that can be detected in the urine of people with tuberculous disease (Bjerrum 2019). This urine test offers potential advantages over sputum-based testing due to ease of sample collection. The accuracy of urinary LAM detection is improved among people living with HIV with advanced immunosuppression (Bjerrum 2019; Nicol 2014; Shah 2016b). In two randomized trials, the use of lateral flow urine lipoarabinomannan assay (LF-LAM) in HIV-positive adult inpatients was shown to reduce mortality (Gupta-Wright 2018; Peter 2016). Based on evidence from randomized trials and from a Cochrane Review (Bjerrum 2019), the WHO recommends that LF-LAM (Alere Determine™ TB LAM Ag, Alere Inc, Waltham, MA, USA) was the only product available at the time of this recommendation and should be used to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children. The full recommendations, which differ for inpatients and outpatients, are described at WHO Lateral flow LAM 2019. However, the evidence for LF-LAM in children is limited and is primarily extrapolated from adults. A new urine-based, point-of-care LAM test, Fujifilm SILVAMP TB LAM (FujiLAM, co-developed by FIND, Geneva, Switzerland, and Fujifilm, Tokyo, Japan), for diagnosis of tuberculosis, is currently under investigation and has the potential to increase sensitivity in children (Broger 2019).

The quest for novel and more efficient technologies for diagnosis of tuberculosis is a cornerstone of current efforts to reduce the burden of disease worldwide. Over the past decade, unprecedented activity has focused on the development of new tools for diagnosis of extrapulmonary tuberculosis, largely supported by the engagement of global agencies. As a result, a strong pipeline of new tools for diagnosis of tuberculosis will complement the use of existing ones and will offer improved options (Boyle 2017).

Rationale

Timely and reliable diagnosis of tuberculosis in children remains challenging due to both difficulties in collecting sputum samples and the paucibacillary nature of the disease. As a result, undiagnosed cases of disease increase morbidity, mortality, and disease transmission in this key group.

We are aware of two systematic reviews that determined the diagnostic accuracy of Xpert MTB/RIF for tuberculosis in children. Wang 2015 (literature searched up to 28 October 2014) included 11 studies (3801 children) and found that Xpert MTB/RIF had pooled sensitivity and specificity (95% confidence interval) of 65% (61% to

69%) and 99% (98% to 99%) against a culture reference standard. Detjen 2015 (literature searched up to 6 January 2015) included 15 studies (3640 children). Similar to Wang 2015, Detjen 2015 found that sputum Xpert MTB/RIF had pooled sensitivity and specificity (95% credible interval) of 62% (51% to 73%) and 98% (97% to 99%) against culture.

In 2013, informed in part by the Detjen 2015 review, the WHO recommended the use of Xpert MTB/RIF for children as a front-line test for diagnosis. In preparation for a WHO meeting to update recommendations on the use of molecular tests for active tuberculosis, we performed a Cochrane Review to update the literature, assess the accuracy of both Xpert MTB/RIF and Xpert Ultra, and address limitations noted in the prior reviews, in particular, the small number of included studies and the predominance of hospitalised children.

OBJECTIVES

Primary objectives

- To determine the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for (a) pulmonary tuberculosis in children presumed to have tuberculosis; (b) tuberculous meningitis in children presumed to have tuberculosis; (c) lymph node tuberculosis in children presumed to have tuberculosis; and (d) rifampicin resistance in children presumed to have tuberculosis
  - For tuberculosis detection, index tests were used as the initial test, replacing standard practice (i.e. smear microscopy or culture)
  - For detection of rifampicin resistance, index tests replaced culture-based drug susceptibility testing as the initial test

Secondary objectives

- To compare the accuracy of Xpert MTB/RIF and Xpert Ultra for each of the four target conditions
- To investigate potential sources of heterogeneity in accuracy estimates
  - For tuberculosis detection, we considered age, disease severity, smear-test status, HIV status, clinical setting, specimen type, high tuberculosis burden, and high tuberculosis/HIV burden
  - For detection of rifampicin resistance, we considered multi-drug-resistant tuberculosis burden
- To compare multiple Xpert MTB/RIF or Xpert Ultra results (repeated testing) with the initial Xpert MTB/RIF or Xpert Ultra result

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional studies, cohort studies, and randomized controlled trials from all settings. We included randomized controlled trials that evaluated use of the test for patient health outcomes but also reported sensitivity and specificity. Although the study was a randomized trial for the purpose of determining the impact of the test versus a comparator (e.g. usual practice, another test) on health outcomes, the study design was a cross-sectional design for the purpose of determining diagnostic accuracy for the index tests in this review. We included only studies from which we could extract or derive data on the index test being a true-positive, a false-positive, a true-negative, or a false-negative as measured against the reference standards specified below. We excluded case-control studies and case reports. We used abstracts to identify published studies and included those that met the inclusion criteria.

Participants

We included studies that evaluated the index tests for pulmonary or extrapulmonary tuberculosis in HIV-positive and HIV-negative children aged 0 to 14 years presumed to have tuberculosis. Studies were eligible for inclusion if they described the use of Xpert MTB/RIF or Xpert Ultra on routine respiratory specimens such as expectorated or induced sputum and gastric and nasopharyngeal specimens. Gastric specimens could be obtained via gastric aspiration, lavage, or washing as described by study authors. We included studies that evaluated bronchoalveolar lavage specimens. In addition, we included studies evaluating stool specimens because tuberculosis bacilli are present in swallowed sputum and are recoverable from stool samples using Xpert MTB/RIF or Xpert Ultra. We also included studies that assessed several different specimen types.

Index tests

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

Index test results are automatically generated, and the user is provided with a printable test result as follows.

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

Xpert Ultra incorporates a semi-quantitative classification for results: trace, very low, low, moderate, and high. 'Trace' corresponds to the lowest bacterial burden for detection of *M tuberculosis* (Chakravorty 2017). Although no rifampicin resistance result will be available for patients with trace results, a trace-positive result is sufficient to initiate anti-tuberculosis therapy in children or HIV-positive patients, according to the WHO report (WHO 2017). Hence, we considered a trace result to mean *M tuberculosis* DETECTED.

Target conditions

The target conditions were active pulmonary tuberculosis; two forms of extrapulmonary tuberculosis - lymph node tuberculosis and tuberculous meningitis; and rifampicin resistance.

Reference standards

For detection of pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis, we included two reference standards.

- Culture: tuberculosis was defined as a positive culture on solid or liquid medium.
- Composite reference standard: tuberculosis was defined as a positive culture or a clinical decision, based on clinical features, to initiate treatment for tuberculosis (i.e. clinically diagnosed tuberculosis). Clinical features might include cough longer than two weeks, fever, or weight loss; pneumonia that did not improve with antibiotics; or a history of close contact with an adult who had tuberculosis.
  * In the absence of information on tuberculosis treatment, for the composite reference standard, we accepted a study-specific definition (i.e. a standardized definition of tuberculosis defined by the primary study authors), if available.
  * For the composite reference standard, when information about tuberculosis treatment was not available, we accepted the uniform research definition (Graham 2012; Graham 2015). In these situations, using the older definition (Graham 2012), we defined tuberculosis as:
    - ☐ confirmed, probable, and possible cases; and
    - ☐ non-tuberculosis.
- For the newer definition (Graham 2015), we used the categories tuberculosis confirmed and not confirmed.
  * In cases where a study-specific definition for the composite references standard was applied, this was accepted as well.

A child was considered as 'not tuberculosis' if the culture result was negative. In the absence of a culture result, a child was considered 'not tuberculosis' if an alternative diagnosis was established, his or her symptoms resolved without tuberculosis treatment, or he or she did not progress to tuberculosis disease after at least one month.

Children with unconfirmed tuberculosis were included among the true-negative population when evaluated against a culture reference standard. In contrast, children who were not treated for tuberculosis, or who did not meet the study research definition for tuberculosis, were included in the true-negative population when evaluated against a composite reference standard.

Regarding stool specimens (used for the diagnosis of pulmonary tuberculosis), we defined the reference standard as in MacLean 2019: (1) culture, or (2) Xpert MTB/RIF or Xpert Ultra performed on a routine respiratory specimen, such as sputum or gastric aspirate specimen. Stool Xpert MTB/RIF and stool Xpert Ultra were not included in the definition of the reference standard. In addition, none of the included studies used stool culture to verify pulmonary tuberculosis. For these reasons, we thought bias due to incorporation of the index test was unlikely. Hence, tuberculosis was defined as a positive culture or a positive Xpert MTB/RIF or a positive Xpert Ultra on a routine respiratory specimen.

Regarding stool specimens, we also included a composite reference standard as defined above.

Culture is generally considered the best reference standard for tuberculosis diagnosis. However, particularly in children with paucibacillary disease, tuberculosis is verified by culture in only 15% to 50% of cases, depending on disease severity, challenges of obtaining specimens, and resources (Graham 2015). Evaluation of multiple specimens, of the same or different types, may increase the yield of culture for confirming tuberculosis (Cruz 2012; Zar 2012). Therefore, we considered a higher-quality reference standard to be one in which more than one specimen was used to confirm tuberculosis. We considered a lower-quality reference standard to be one in which only one specimen was used for tuberculosis diagnosis. We reflected these considerations in the Quality Assessment of Studies of Diagnostic Accuracy - Revised (QUADAS-2), Reference Standard domain.

For rifampicin resistance, the reference standards were phenotypic drug susceptibility testing and MTBDR*plus*. MTBDR*plus* is a molecular line probe assay designed to detect the presence of multiple mutations causing resistance to isoniazid and rifampicin.

Search methods for identification of studies

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

Electronic searches

We searched the following databases up to 29 April 2019 using the search terms and strategy described in Appendix 1.

- Cochrane Infectious Diseases Group Specialized Register.
- MEDLINE (OVID, from 1966).
- Embase (OVID, from 1974).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL (EBSCOHost), from 1982).
- Science Citation Index - Expanded (from 1900), Conference Proceedings Citation Index - Science (CPCI-S, from 1990), from the Web of Science (Clarivate Analytics).
- Scopus (Elsevier, from 1970).

We also searched ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch), and the International Standard Randomized Controlled Trials Number (ISRCTN) Registry (www.isrctn.com/) for trials in progress, up to 28 January 2020.

Searching other resources

We contacted researchers and experts in the field to identify additional eligible studies. We checked the references of relevant reviews and studies to identify additional studies.

Data collection and analysis

Selection of studies

Two review authors independently screened all titles and abstracts to identify potentially eligible studies. We then obtained the full-text articles of potentially eligible studies, and two review authors independently assessed whether they should be included based on pre-defined inclusion and exclusion criteria. We resolved disagreements by discussion or by consultation with a third review author if necessary. We contacted study authors for clarification of methods and other information as needed. We recorded and summarized reasons for excluding studies in a Characteristics of excluded studies table. We illustrated the study selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

We designed a data extraction form and piloted it on two included studies (Appendix 2); we then finalized the form based on the pilot test. As above, two review authors independently extracted data using this data extraction form and discussed inconsistencies to achieve consensus. We consulted a third review author to resolve discrepancies as needed. We entered abstracted data into an Excel database on password-protected computers (Excel 2013). We secured the data set in a cloud storage workspace (Dropbox), and we stored extracted data for future review updates. Selected details of data extraction are listed below.

Study details

- Number of participants after screening for exclusion and inclusion criteria
- Total number of children included in the analysis
- Total number of specimens included with collection methods
- Unit of sample collection: one specimen, multiple specimens, unknown, or unclear
- Percentage (numerator/denominator) of children with prior tuberculosis
- Target condition(s)? - pulmonary tuberculosis, lymph node tuberculosis, tuberculous meningitis, rifampicin resistance

Patient characteristics and setting

- Description of study population
- Age: median, mean, range, and disaggregation into categories (0 to 4, 5 to 14)
- Gender
- HIV status
- Smear status
- Percentage and number of HIV-positive or HIV-negative participants, if both were included in the study
- Type of respiratory specimen included: expectorated, induced, nasopharyngeal aspirate, gastric lavage, stool
- Type of non-respiratory specimen included: fine needle aspirate, lymph node biopsy, cerebrospinal fluid, multiple types, other, unknown
- Number of cultures performed per child to exclude tuberculosis
- Data on culture performance: number of contaminated cultures with respect to total cultures performed
- Clinical setting: outpatient or inpatient or both
- Description of radiographic findings
- Information on tuberculosis burden in the country

We classified 'country' as being high burden or not high burden for tuberculosis, tuberculosis/HIV, or multi-drug-resistant tuberculosis according to the WHO post-2015 era classification (WHO Global TB Report 2019). A country could be classified as high burden for one, two, or all three of the high-burden categories.

Index tests

- Xpert cartridge: MTB/RIF or Ultra
- Pretreatment processing procedure for specimens used for Xpert MTB/RIF or Xpert Ultra
- Specimen condition: fresh, frozen, or both
- Numbers of true-positives, false-positives, false-negatives, and true-negatives (see example table in Appendix 3)
- Uninterpretable results for tuberculosis detection (invalid, error, or no result)
- Indeterminate results for detection of rifampicin resistance

Reference standards

- Details of culture - solid or liquid
- Composite reference standard - description
- Rifampicin resistance - phenotypic drug susceptibility testing or MTBDR*plus*

For each target condition and specimen type, we considered one index test result per child. Hence, the primary unit of analysis was the patient. If studies evaluated more than one specimen type, we extracted data for each specimen. Hence, a study may have contributed more than one 2 × 2 table (data set) - one for each type of specimen evaluated.

Assessment of methodological quality

We assessed the methodological quality of included studies using the QUADAS-2 instrument, which we adapted for this review (Whiting 2011). The QUADAS-2 tool consists of four domains: (1) patient selection, (2) index test(s), (3) reference standard(s), and (4) flow and timing. All domains are assessed for risk of bias, and the first three domains for concerns regarding applicability. We first developed guidance on how to appraise each signalling question within the domains and how to make the overall judgement for each domain. One review author piloted the tool with two of the included studies. We finalized the guidance based on experience gained from the pilot. The QUADAS-2 tool with signalling questions tailored to this review is provided in Appendix 4. Two review authors independently completed QUADAS-2. We resolved disagreements through discussion or by arbitration with a third review author when necessary. We have presented results of the quality assessment in the text, in tables, and in graphs.

Statistical analysis and data synthesis

We performed descriptive analyses of the included studies and presented their key characteristics in the Characteristics of included studies table. We presented individual study estimates of sensitivity and specificity graphically in forest plots and in receiver operating characteristics (ROC) space using Review Manager 5 (Review Manager 2014).

For detection of rifampicin resistance, we included children who:

- were culture-positive;
- had a valid phenotypic drug susceptibility test (DST) result;
- were Xpert tuberculosis-positive; and
- had a valid Xpert rifampicin result.

Sensitivity = Xpert rifampicin resistant/phenotypic or MTBDR*plus* DST rifampicin resistant.
Specificity = Xpert rifampicin susceptible/phenotypic MTBDR*plus* DST rifampicin susceptible.

When data were sufficient, we performed meta-analyses to estimate average sensitivities and specificities using a bivariate model (Chu 2006; Reitsma 2015). We used the bivariate model because the index tests, Xpert MTB/RIF, and Xpert Ultra all apply

a common positivity criterion (Macaskill 2010). When we were unable to fit a bivariate model due to sparse data, few studies, or little observed variability in specificity, we simplified the model to a univariate random-effects logistic regression model to pool sensitivity and specificity separately (Takwoingi 2015). For the analysis of Xpert MTB/RIF in the subgroup of smear-positive children, we performed a univariate analysis of only sensitivity. We did this because studies or subgroups of smear-positive children had few or zero false-positives and true-negatives; thus pooling specificity was not meaningful. We performed meta-analyses using the meqrlogit command in Stata version 15 (Stata 15). We stratified all analyses by type of reference standard. For rifampicin resistance detection, we identified few studies evaluating Xpert MTB/RIF and zero studies evaluating Xpert Ultra. Therefore, we analysed all specimen types together.

We performed comparative meta-analyses by restricting the analyses to only those studies that made direct comparisons between Xpert MTB/RIF and Xpert Ultra within the same participants. We performed comparative meta-analyses using meta-regression by including test type as a covariate in a bivariate model. We assessed model fit using likelihood ratio tests to compare models with and without the covariate terms. We calculated absolute differences in sensitivity and specificity using the bivariate model parameters. We obtained 95% confidence intervals and P values for the absolute differences using the delta method and Wald tests, respectively. We performed additional comparative analyses in which we compared the accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis on repeated testing versus a first test.

Approach to uninterpretable index test results

Xpert MTB/RIF and Xpert Ultra report an uninterpretable test result for unexpected results with any of the internal control measures of the assay. The uninterpretable rate for detection of tuberculosis is the number of tests classified as "invalid", "error", or "no result" divided by the total number of Xpert tests performed. The indeterminate rate for detection of rifampicin resistance is the number of tests classified as "MTB DETECTED; Rif resistance INDETERMINATE" divided by the total number of Xpert-positive results. We had planned to estimate the pooled proportion of uninterpretable Xpert MTB/RIF and Xpert Ultra results for tuberculosis detection and indeterminate Xpert MTB/RIF and Xpert Ultra results for detection of rifampicin resistance. We were unable to perform the analyses owing to limited data, but we have summarized these results in a table along with the key characteristics of included studies.

Investigations of heterogeneity

We visually inspected forest and summary ROC plots for heterogeneity. When data allowed, we evaluated sources of heterogeneity using subgroup analyses and meta-regression. We were interested in tests performed in key subgroups of children: age zero to four years, age 5 to 14 years, smear-positive, smear-negative, HIV-positive, and HIV-negative. For tuberculosis detection, we performed bivariate meta-regression with the following potential sources of heterogeneity as a single covariate in the model.

- High tuberculosis burden: yes or no.
- High tuberculosis/HIV burden: yes or no.
- Cultures used to verify tuberculosis: multiple or single.

Detection of rifampicin resistance

We had planned to perform bivariate meta-regression while considering high multi-drug-resistant tuberculosis burden as a potential source of heterogeneity, but we were unable to perform this analysis owing to limited data.

Sensitivity analyses

Data were sufficient for sensitivity analyses to explore the effects of risk of bias items and study characteristics on pooled estimates of the accuracy of Xpert MTB/RIF. Such analyses were possible only for studies that used sputum as the specimen. We limited the meta-analyses to the following.

- Studies that used consecutive or random selection of participants.
- Studies in which the reference standard results were interpreted without knowledge of the index test results.
- Studies that included only untreated patients.
- Studies that explicitly reported enrolling children 0 to 14 years old.

In addition, for studies in which gastric aspirate specimens and sputum specimens were collected, data were included with the sputum analyses within the main analyses; so we performed a sensitivity analysis excluding these studies.

Assessment of reporting bias

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

Assessment of certainty of the evidence

We assessed certainty of the evidence by using the GRADE approach for diagnostic studies (Balshem 2011; Schünemann 2008; Schünemann 2016). As recommended, we rated certainty of the evidence as high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) based on five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each outcome, certainty of the evidence started as high when high-quality studies (cross-sectional or cohort studies) enrolled participants with diagnostic uncertainty. If we found a reason for downgrading, we used our judgement to classify the reason as serious (downgraded by one level) or very serious (downgraded by two levels).

Three review authors (AWK, LGF, and KRS) discussed judgements and applied GRADE in the following way (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 pre-specified analyses to investigate potential sources of heterogeneity and downgraded when we could not explain inconsistency in accuracy estimates.

Imprecision

We considered a precise estimate to be one that would allow a clinically meaningful decision. We considered the width of the confidence interval (CI) and asked, "Would we make a different decision if the lower or upper boundary of the CI represented the truth?" In addition, we worked out projected ranges for true-positive (TP), false-negative (FN), true-negative (TN), and false-positive (FP) for a given prevalence of tuberculosis and made judgements on imprecision from these calculations.

Publication bias

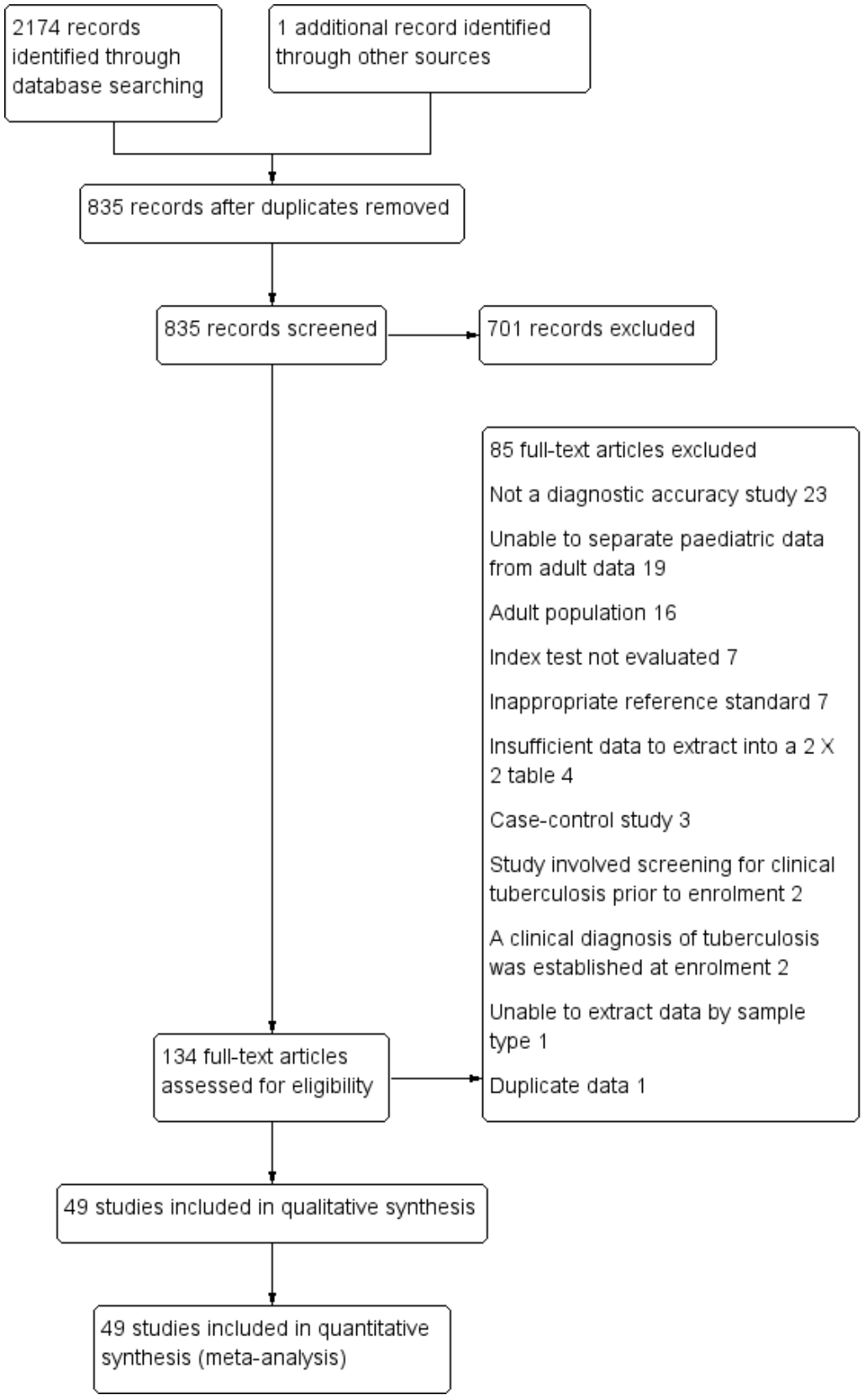
We rated publication bias as undetected (not serious) for several reasons including comprehensiveness of the literature search and extensive outreach to tuberculosis researchers to identify studies.

RESULTS

Results of the search

We identified 2174 records through database searches conducted up to 29 April 2019 and one additional record identified through other sources. After excluding duplicate records, we scrutinized the titles and abstracts of 835 records and excluded 701 records for relevance. We retrieved 134 articles and, after full-text review, included 49 studies in the review (Anderson 2014; Andriyoko 2019; Atwebembeire 2016; Bacha 2017; Bates 2013; Bhatia 2016; Bholla 2016; Brent 2017; Bunyasi 2015; Causse 2011; Chipinduro 2017; Chisti 2014; Coetzee 2014; Das 2019; Gous 2015; Hanrahan 2018; Hasan 2017; Kasa Tom 2018; Kim 2015; LaCourse 2014; LaCourse 2018; Ligthelm 2011; Malbruny 2011; Marcy 2016; Moussa 2016; Myo 2018; Nhu 2013; Nicol 2011; Nicol 2013; Nicol 2018; Orikiriza 2018; Pang 2014; Rachow 2012; Reither 2015; Sabi 2018; Saini 2018; Sekadde 2013; Singh M 2016; Solomons 2015; Togun 2015; Tortoli 2012; Vadwai 2011; Walters 2014; Walters 2017a; Walters 2018a; Yin 2014; Zar 2012; Zar 2013; Zar 2019) See Characteristics of included studies. All studies were written in English. Figure 2 shows the flow of studies in the review. We recorded the excluded studies and reasons for their exclusion in the Characteristics of excluded studies table.

Figure 2. Study flow diagram.



The 49 studies included one randomized trial, 20 cohort studies, and 28 cross-sectional studies. Thirty-nine studies (80%) took place in countries with high tuberculosis burden and 39 (80%) in countries with high TB/HIV burden. Most studies (30/49; 61%) used liquid culture for the reference standard (Table 1).

For pulmonary tuberculosis, 299 data sets (68,544 participants) were available for analysis; for tuberculous meningitis, 10 data sets (423 participants) were available; for lymph node tuberculosis, 10 data sets (318 participants) were available; and for rifampicin resistance, 14 data sets (326 participants) were available.

Methodological quality of included studies

Pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis

Figure 3 and Figure 4 show risk of bias and applicability concerns for 49 studies that evaluated Xpert MTB/RIF and Xpert Ultra for detection of pulmonary tuberculosis, tuberculous meningitis, or lymph node tuberculosis.

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

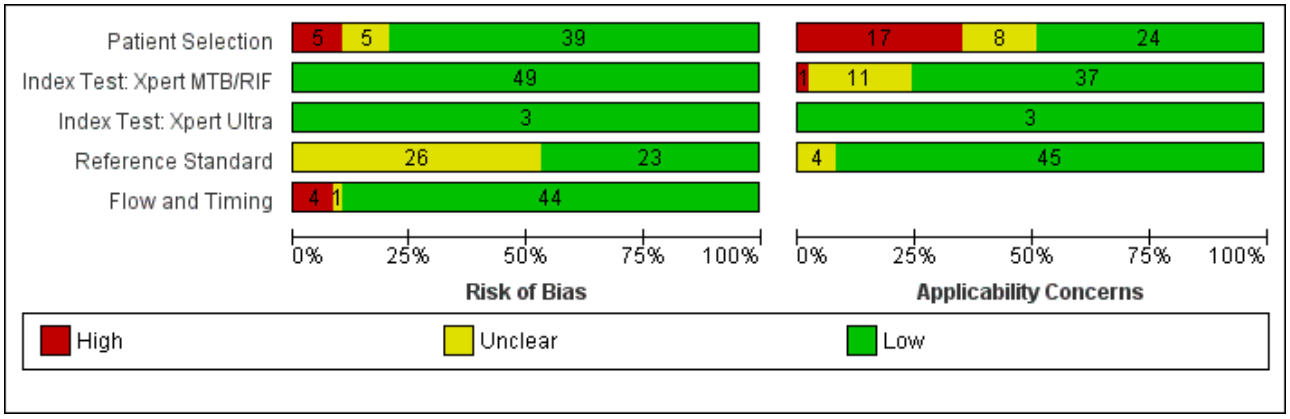


Figure 4. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

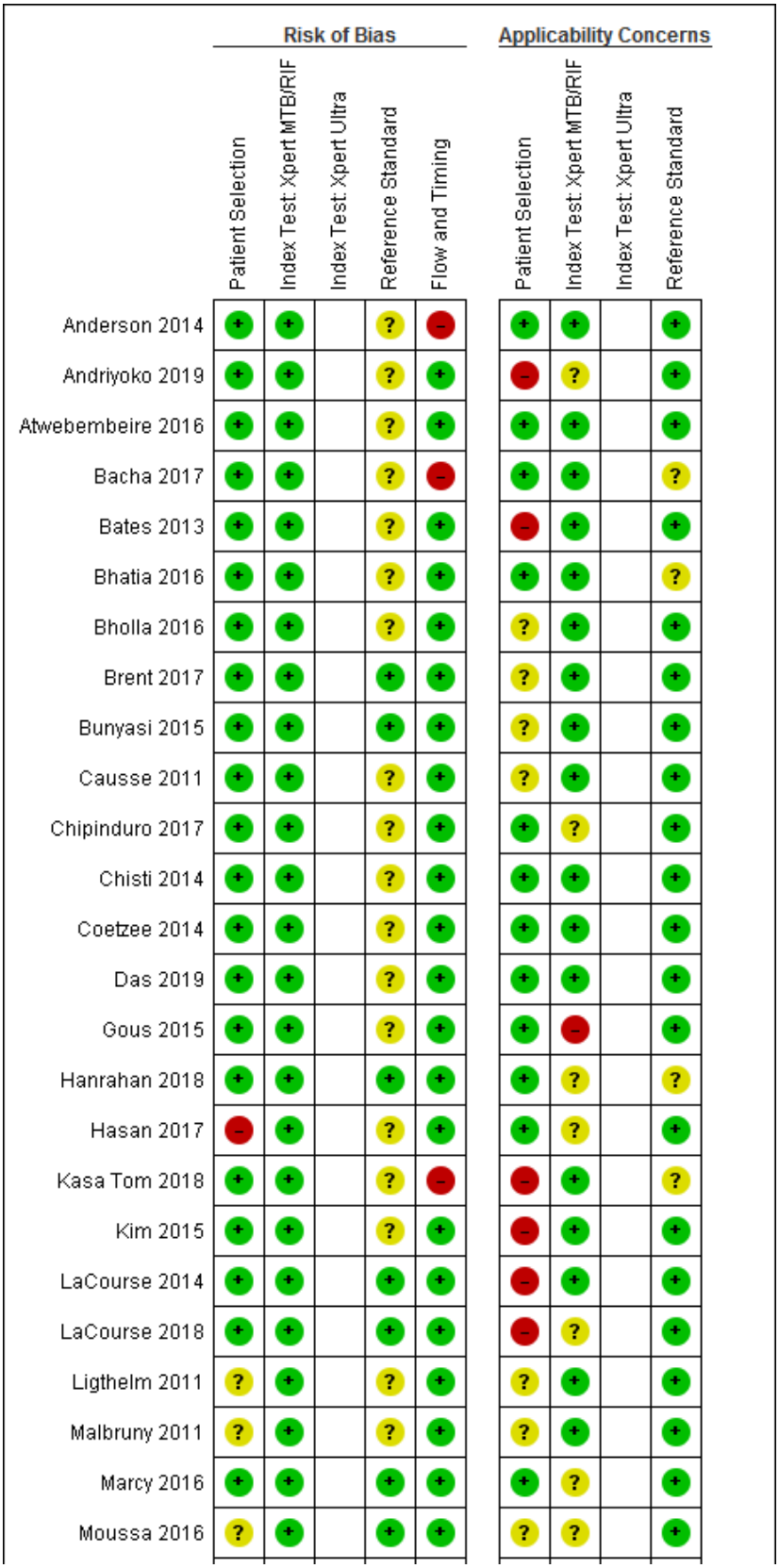
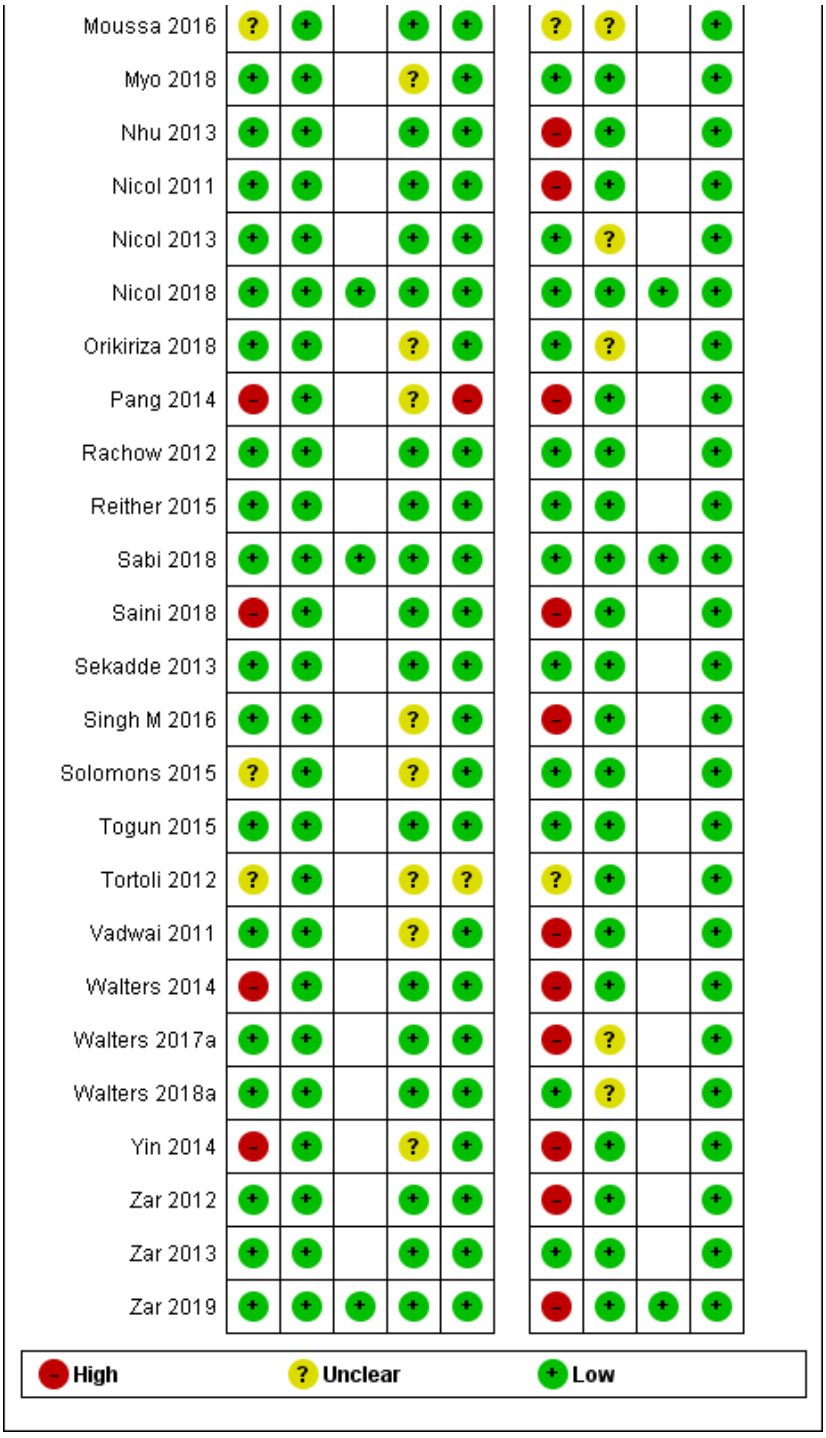


Figure 4. (Continued)



In the Patient Selection domain, we considered 39 studies (80%) to have low risk of bias because studies enrolled a consecutive or random sample of eligible participants and avoided inappropriate exclusions. We considered five studies (10%) to have high risk of bias because they did not avoid inappropriate exclusions: one study enrolled participants whose sputum specimens were primarily or exclusively smear-positive or smear-negative (Pang 2014); three studies enrolled only participants with negative testing for tuberculosis before performance of bronchoalveolar lavage (Saini 2018; Walters 2014; Yin 2014); and one study enrolled patients using a convenience sample (Hasan 2017). In addition, we considered five studies to have unclear risk of bias because the manner of participant selection was not stated (Ligthelm 2011; Malbruny 2011; Moussa 2016; Solomons 2015; Tortoli 2012). With respect to applicability, we considered 24 studies (49%) to have low concern because participants in these studies were evaluated

in primary care facilities, in local hospitals, or in both settings (Anderson 2014; Atwebembeire 2016; Bacha 2017; Bhatia 2016; Chipinduro 2017; Chisti 2014; Coetzee 2014; Das 2019; Gous 2015; Hanrahan 2018; Hasan 2017; Marcy 2016; Myo 2018; Nicol 2013; Nicol 2018; Orikiriza 2018; Rachow 2012; Reither 2015; Sabi 2018; Sekadde 2013; Solomons 2015; Togun 2015; Walters 2018a; Zar 2013). We considered 17 studies (34%) to have high concern because participants were evaluated exclusively as inpatients in tertiary care centres (Andriyoko 2019; Bates 2013; Kasa Tom 2018; Kim 2015; LaCourse 2014; LaCourse 2018; Nhu 2013; Nicol 2011; Pang 2014; Saini 2018; Singh M 2016; Vadwai 2011; Walters 2014; Walters 2017a; Yin 2014; Zar 2012; Zar 2019). We considered eight studies to have unclear concern because we could not be sure about concerns (Bholla 2016; Brent 2017; Bunyasi 2015; Causse 2011;Ligthelm 2011; Malbruny 2011; Moussa 2016; Tortoli 2012).

In the Index Test domain, we considered all studies to have low risk of bias. With respect to applicability, we considered 37 studies (76%) to have low concern and one study to have high concern because the ratio of sample reagent to specimen volume differed from that recommended by the manufacturer (Gous 2015). We also considered all 11 studies (22%) that evaluated stool specimens to have unclear concern because of the absence of an established protocol for stool processing before Xpert MTB/RIF testing (Andriyoko 2019; Chipinduro 2017; Hanrahan 2018; Hasan 2017; LaCourse 2018; Marcy 2016; Moussa 2016; Nicol 2013; Orikiriza 2018; Walters 2017a; Walters 2018a).

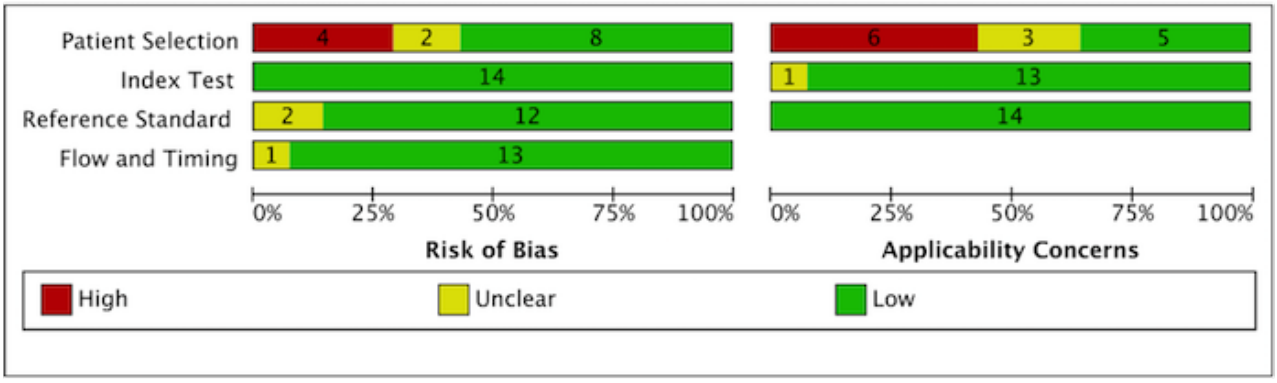
In the Reference Standard domain, we considered 23 studies to have low risk of bias and 26 studies (53%) to have unclear risk of bias because the ability of the reference standard to appropriately classify child tuberculosis was uncertain (Anderson 2014; Andriyoko 2019; Atwebembeire 2016; Bacha 2017; Bates 2013; Bhatia 2016; Bholla 2016; Causse 2011; Chipinduro 2017; Chisti 2014; Coetzee 2014; Das 2019; Gous 2015; Hasan 2017; Kasa Tom 2018; Kim 2015; Ligthelm 2011; Malbruny 2011; Myo 2018; Orikiriza 2018; Pang 2014; Singh M 2016; Solomons 2015; Tortoli 2012; Vadwai 2011; Yin 2014). With respect to applicability, we considered 45 studies to have low concern because speciation was performed, confirming *M tuberculosis* instead of other mycobacterial species, and four studies (8%) to have unclear concern because we could not tell whether speciation was performed (Bacha 2017; Bhatia 2016; Hanrahan 2018; Kasa Tom 2018).

In the Flow and Timing domain, we considered 44 studies (90%) to have low risk of bias because all participants were included in the analysis. We considered four studies to have high risk of bias because results of the index or reference tests were not available for many participants (Anderson 2014; Bacha 2017; Kasa Tom 2018; Pang 2014). We considered one study to have unclear risk of bias because we could not tell whether the index and reference tests were collected at appropriate intervals (Tortoli 2012).

Rifampicin resistance

Figure 5 shows risk of bias and applicability concerns for 14 studies evaluating Xpert MTB/RIF for detection of rifampicin resistance.

Figure 5. Risk of bias and applicability concerns graph for rifampicin resistance: review authors' judgements about each domain presented as percentages across included studies.



In the Patient Selection domain, we considered eight studies (57%) to have low risk of bias because studies enrolled a consecutive or random sample of eligible participants and avoided inappropriate exclusions (Bates 2013; Bholla 2016; Chipinduro 2017; Das 2019; Rachow 2012; Reither 2015; Zar 2012; Zar 2013). We considered four studies (29%) to have high risk of bias because studies did not avoid inappropriate exclusions and instead enrolled participants pre-selected on the basis of their sputum specimens being smear-negative or studies exclusively enrolled participants who had negative testing before bronchoalveolar lavage (Pang 2014; Saini 2018; Walters 2014; Yin 2014). We considered two studies (14%) to have unclear risk of bias because the manner of participant selection was not reported (Malbruny 2011; Tortoli 2012). With respect to applicability, we considered five studies (36%) to have low concern because participants in these studies were evaluated in primary care facilities, in local hospitals, or in both settings (Chipinduro 2017; Das 2019; Rachow 2012; Reither 2015; Zar 2013). We considered six studies to have high concern (43%) because participants were evaluated exclusively as inpatients in tertiary care centres (Bates 2013; Pang 2014; Saini 2018; Walters 2014; Yin 2014; Zar 2012). We considered the remaining three studies (21%) to have unclear concern because we could not be sure about concerns (Bholla 2016; Malbruny 2011; Tortoli 2012).

In the Index Test domain, we considered all studies to have low risk of bias. With respect to applicability, we considered 13 studies (93%) to have low concern and one study (7%) that evaluated stool specimens to have unclear concern because of the absence of an established protocol for stool processing before Xpert MTB/RIF testing (Chipinduro 2017).

In the Reference Standard domain, we considered eight studies (57%) to have low risk of bias because results of the reference standard were interpreted without knowledge of results of the index test (Bholla 2016; Chipinduro 2017; Rachow 2012; Reither 2015; Saini 2018; Tortoli 2012; Yin 2014; Zar 2012). We considered the remaining six studies (43%) to have unclear risk of bias because information about blinding was not reported (Bates 2013; Das 2019; Malbruny 2011; Pang 2014; Walters 2014; Zar 2013). With respect to applicability, we considered all studies to have low concern because in these studies, all specimens had already been speciated and identified as *M tuberculosis*.

In the Flow and Timing domain, we considered 12 studies (86%) to have low risk of bias because all participants were included in the analysis. We considered one study (7%) to have high risk of bias because all participants were not included in the analysis (Pang 2014). We considered one study (7%) to have unclear risk of bias because we could not tell if the index and reference tests were collected at appropriate intervals (Tortoli 2012).

Findings

I. Detection of pulmonary tuberculosis

Due to little observed variability in specificity and in the volume of analyses, we chose to present only forest plots, as such plots were more informative than corresponding summary receiver operator characteristics (SROC) plots.

I.A. Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis

I.A.1. Xpert MTB/RIF in sputum - induced or expectorated

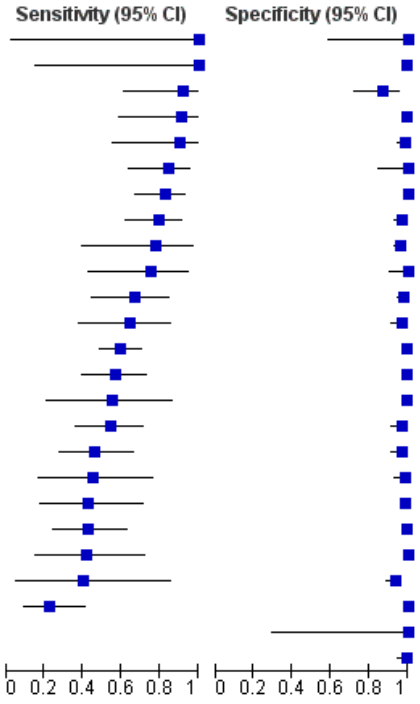
Studies were conducted in Bangladesh, Gambia, India, Kenya, Malawi, South Africa, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe.

I.A.I.a. Culture reference standard

Twenty-five studies (6812 participants) evaluated Xpert MTB/RIF in sputum specimens against culture (Anderson 2014; Atwebembeire 2016; Bacha 2017; Bates 2013; Brent 2017; Bunyasi 2015; Chipinduro 2017; Chisti 2014; Das 2019; Gous 2015; Hanrahan 2018; LaCourse 2014; Malbruny 2011; Nhu 2013; Nicol 2011; Nicol 2013; Orikiriza 2018; Rachow 2012; Reither 2015; Sekadde 2013; Singh M 2016; Togun 2015; Walters 2017a; Zar 2012; Zar 2013). Xpert MTB/RIF sensitivity ranged from 23% to 100%, and specificity from 87% to 100% (Figure 6). Two studies had no cases of tuberculosis, and so sensitivity was not estimable (Hanrahan 2018; Malbruny 2011). In sputum, Xpert MTB/RIF pooled sensitivity and specificity were as follows against culture (95% CI): 64.6% (55.3% to 72.9%) and 99.0% (98.1% to 99.5%).

Figure 6. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in sputum (culture reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

Study	TP	FP	FN	TN	Culture	Sensitivity (95% CI)	Specificity (95% CI)
Das 2019	1	0	0	7	Single	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
LaCourse 2014	2	1	0	297	Multiple	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Singh M 2016	11	5	1	33	Single	0.92 [0.62, 1.00]	0.87 [0.72, 0.96]
Orikiriza 2018	10	3	1	325	Multiple	0.91 [0.59, 1.00]	0.99 [0.97, 1.00]
Bates 2013	9	2	1	130	Single	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Nhu 2013	21	0	4	22	Multiple	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
Brent 2017	33	0	7	1064	Single	0.82 [0.67, 0.93]	1.00 [1.00, 1.00]
Sekadde 2013	27	7	7	194	Single	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
Chipinduro 2017	7	8	2	201	Single	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Nicol 2011	9	0	3	36	Multiple	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Walters 2017a	16	6	8	240	Single	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]
Nicol 2013	11	3	6	95	Multiple	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]
Zar 2012	52	2	35	385	Multiple	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
Reither 2015	21	2	16	411	Multiple	0.57 [0.39, 0.73]	1.00 [0.98, 1.00]
Gous 2015	5	3	4	333	Single	0.56 [0.21, 0.86]	0.99 [0.97, 1.00]
Anderson 2014	19	3	16	96	Multiple	0.54 [0.37, 0.71]	0.97 [0.91, 0.99]
Rachow 2012	13	3	15	98	Multiple	0.46 [0.28, 0.66]	0.97 [0.92, 0.99]
Atwebembeire 2016	5	1	6	73	Single	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]
Togun 2015	6	6	8	467	Single	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Zar 2013	12	1	16	280	Multiple	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]
Bacha 2017	5	0	7	252	Single	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]
Chisti 2014	2	14	3	192	Single	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
Bunyasi 2015	7	0	24	908	Multiple	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Malbruny 2011	0	0	0	3	Single	Not estimable	1.00 [0.29, 1.00]
Hanrahan 2018	0	1	0	105	Multiple	Not estimable	0.99 [0.95, 1.00]

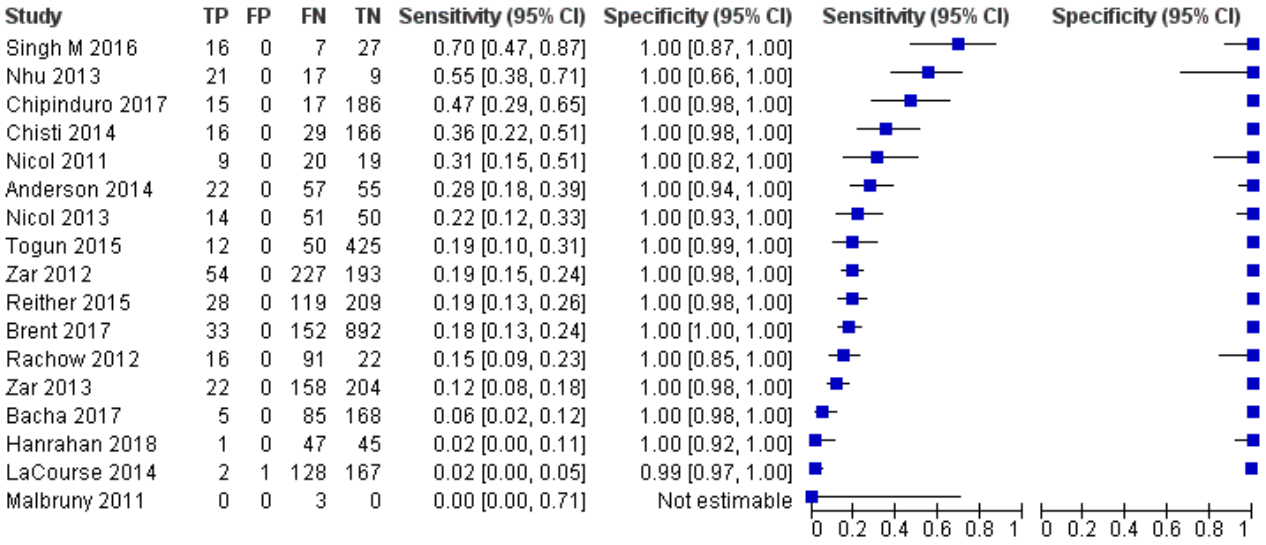


I.A.I.b. Composite reference standard

Seventeen studies (4382 participants) evaluated Xpert MTB/RIF in sputum specimens against a composite reference standard (Anderson 2014; Bacha 2017; Brent 2017; Chipinduro 2017; Chisti 2014; Hanrahan 2018; LaCourse 2014; Malbruny 2011; Nhu 2013; Nicol 2011; Nicol 2013; Rachow 2012; Reither 2015; Singh M 2016; Togun 2015; Zar 2012; Zar 2013) (Figure 7). Malbruny 2011 had no cases without tuberculosis, and so specificity was not estimable. In sputum, Xpert MTB/RIF pooled sensitivity and specificity were

as follows against a composite reference standard (95% CI): 19.7% (12.1% to 30.4%) and 100% (99.8% to 100%) (Table 2).

Figure 7. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in sputum (composite reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



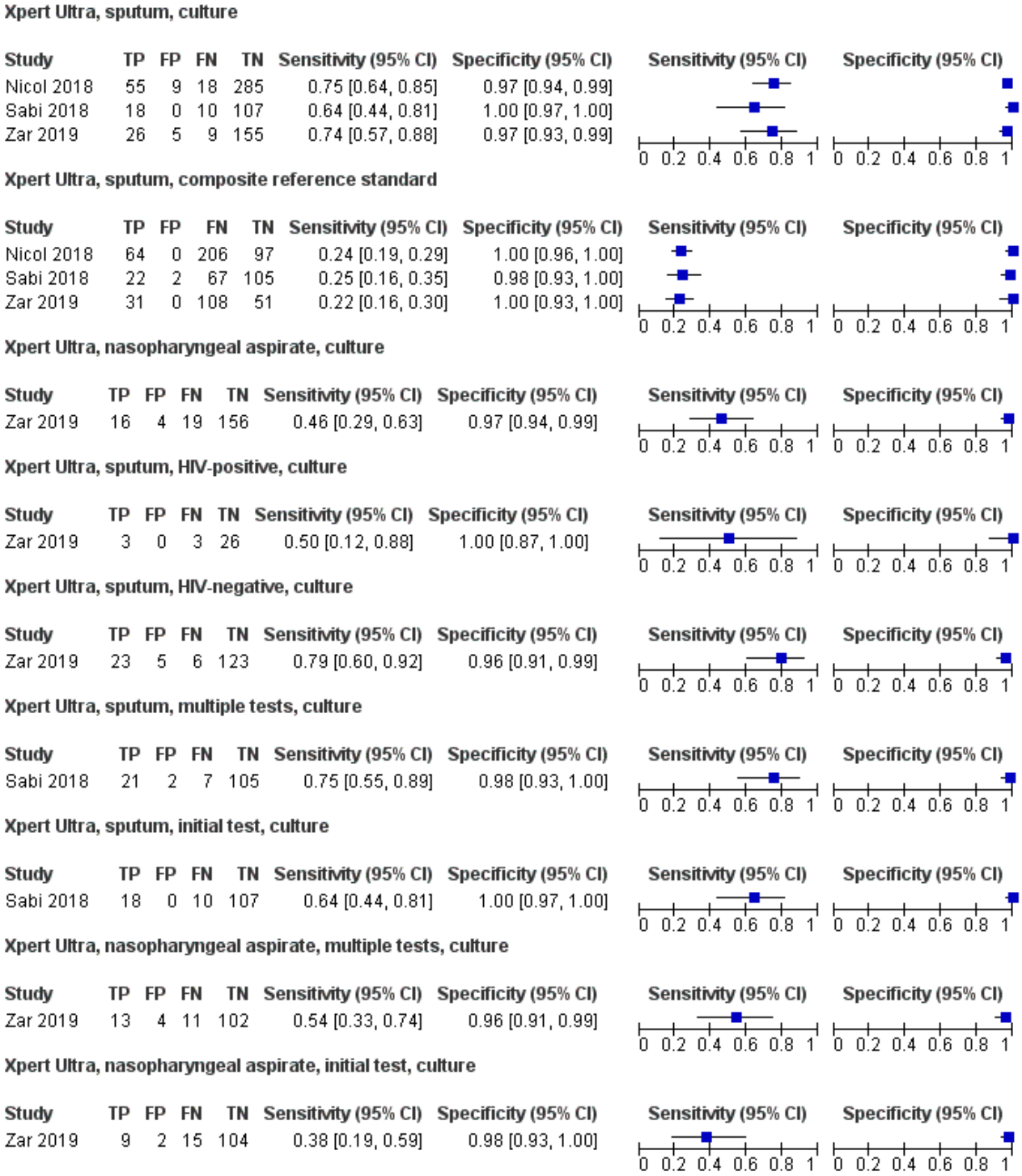
I.B. Xpert Ultra in sputum

Studies were conducted in South Africa and Tanzania.

I.B.1.a. Culture reference standard

Three studies (697 participants) evaluated Xpert Ultra in sputum specimens against culture (Nicol 2018; Sabi 2018; Zar 2019). Xpert Ultra sensitivity ranged from 64% to 75%, and specificity from 97% to 100% (Figure 8). Xpert Ultra pooled sensitivity and specificity were as follows in sputum specimens (95% CI): 72.8% (64.7% to 79.6%) and 97.5% (95.8% to 98.5%) (Table 2).

Figure 8. Forest plots of Xpert Ultra sensitivity and specificity for pulmonary tuberculosis by specimen type, reference standard, HIV status, and results of testing using multiple specimens compared to one specimen (culture reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



I.B.2.b. Composite reference standard

Three studies (753 participants) evaluated Xpert Ultra in sputum specimens against a composite reference standard (Nicol 2018;

Sabi 2018; Zar 2019) (Figure 8). Xpert Ultra pooled sensitivity and specificity were as follows against a composite reference standard (95% CI): 23.5% (20.0% to 27.4%) and 99.2% (96.9% to 99.8%) (Table 2).

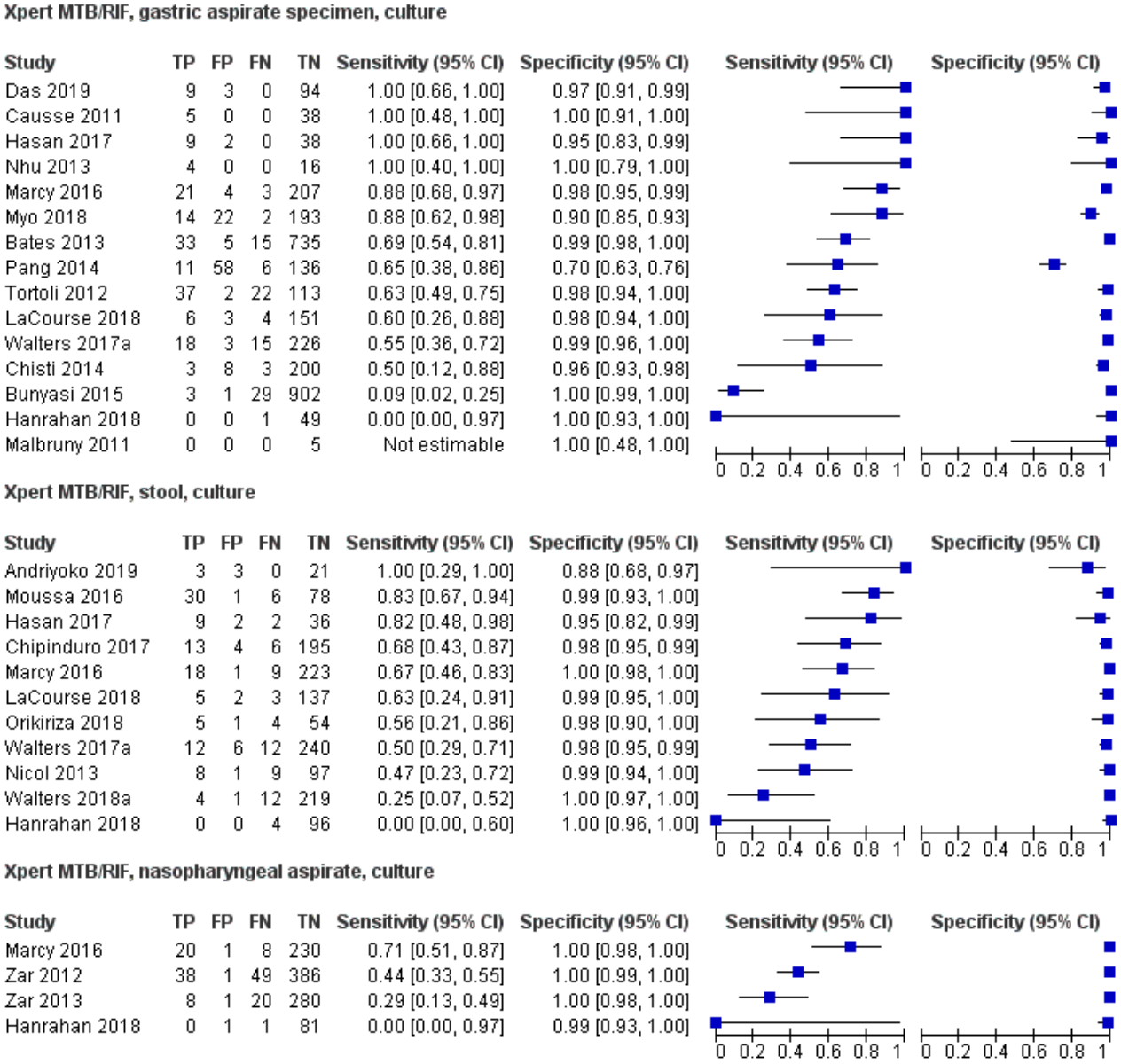
I.A.2. Xpert MTB/RIF in gastric aspirate specimens

Studies were conducted in Bangladesh, Burkina Faso, Cambodia, Cameroon, China, India, Italy, Kenya, Myanmar, Pakistan, South Africa, Spain, Vietnam, and Zambia.

I.A.2.a. Culture reference standard

Fifteen studies (3487 participants) evaluated Xpert MTB/RIF in gastric aspirate specimens against culture (Bates 2013; Bunyasi 2015; Causse 2011; Chisti 2014; Das 2019; Hanrahan 2018; Hasan 2017; LaCourse 2018; Malbruny 2011; Marcy 2016; Myo 2018; Nhu 2013; Pang 2014; Tortoli 2012; Walters 2017a (Figure 9). Malbruny 2011 had no cases with tuberculosis, and so sensitivity was not estimable. Xpert MTB/RIF sensitivity ranged from 0% to 100%, and specificity from 90% to 100%. In gastric aspirate specimens, Xpert MTB/RIF pooled sensitivity and specificity against culture were as follows (95% CI): 73.0% (52.9% to 86.7%) and 98.1% (95.5% to 99.2%) (Table 2).

Figure 9. Forest plots of tests Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in gastric aspirate specimens, stool specimens, and nasopharyngeal aspirates (culture reference standard).The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



I.A.2.b. Composite reference standard

Seven studies (948 participants) evaluated Xpert MTB/RIF in gastric aspirate specimens against a composite reference standard (Chisti 2014; Hasan 2017; Kasa Tom 2018; LaCourse 2018; ; Nhu 2013; Pang 2014). Nhu 2013 had no cases without tuberculosis, and so specificity was not estimable. In gastric aspirate specimens, Xpert MTB/RIF pooled sensitivity and specificity against a composite reference standard were as follows (95% CI): 31.7% (20.2% to 46.0%) and 99.7% (97.1% to 100%) (Table 2).

I.B.2. Xpert Ultra in gastric aspirate specimens

We did not identify any studies that evaluated Xpert Ultra in gastric aspirate specimens, against culture or against a composite reference standard.

I.A.3. Xpert MTB/RIF in stool specimens

Studies were conducted in Burkina Faso, Cambodia, Cameroon, Egypt, Indonesia, Kenya, Pakistan, South Africa, Uganda, Vietnam, and Zimbabwe.

1.A.3.a. Culture reference standard

Eleven studies (1592 participants) evaluated Xpert MTB/RIF in stool specimens against culture (Andriyoko 2019; Chipinduro 2017; Hanrahan 2018; Hasan 2017; LaCourse 2018; Marcy 2016; Moussa 2016; Nicol 2013; Orikiriza 2018; Walters 2017a; Walters 2018a) (Figure 9). In stool specimens, Xpert MTB/RIF pooled sensitivity and specificity against culture were as follows (95% CI): 61.5% (44.1% to 76.4%) and 98.5% (97.0% to 99.2%) (Table 2).

I.A.3.b. Composite reference standard

Ten studies (1739 participants) evaluated Xpert MTB/RIF in stool specimens against a composite reference standard (Chipinduro 2017; Hanrahan 2018; Hasan 2017; LaCourse 2018; Marcy 2016; Moussa 2016; Nicol 2013; Orikiriza 2018; Walters 2017a; Walters 2018a). In stool specimens, Xpert MTB/RIF pooled sensitivity and specificity against a composite reference standard were as follows (95% CI): 16.3% (8.4% to 29.2%) and 99.7% (97.8% to 100%) (Table 2).

I.B.3. Xpert Ultra in stool specimens

We did not identify any studies that evaluated Xpert Ultra in stool specimens against culture or a composite reference standard.

I.A.4. Xpert MTB/RIF in nasopharyngeal specimens

Studies were conducted in Burkina Faso, Cambodia, Cameroon, Vietnam, and South Africa.

1.A.4.a. Culture reference standard

Four studies (1125 participants) evaluated Xpert MTB/RIF in nasopharyngeal specimens against culture (Hanrahan 2018; Marcy 2016; Zar 2012; Zar 2013) (Figure 9). In nasopharyngeal specimens, Xpert MTB/RIF pooled sensitivity and specificity against culture were as follows (95% CI): 45.7% (27.6% to 65.1%) and 99.6% (98.9% to 99.8%) (Table 2).

I.A.4.b. Composite reference standard

For Xpert MTB/RIF, we did not extract data on nasopharyngeal specimens against a composite reference standard.

I.B.4. Xpert Ultra in nasopharyngeal specimens

1.B.4.a. Culture reference standard

One study evaluated Xpert Ultra in nasopharyngeal specimens against culture. Xpert Ultra sensitivity and specificity (95% CI) were 45.7% (28.9% to 63.3%) and 97.5% (93.7% to 99.3%), respectively (Zar 2019) (Figure 8).

I.B.4.b. Composite reference standard

For Xpert Ultra, we did not extract data on nasopharyngeal specimens against a composite reference standard.

I.C. Xpert Ultra versus Xpert MTB/RIF

Three studies compared Xpert Ultra and Xpert MTB/RIF in frozen sputum specimens against a reference standard of culture on a sputum specimen (Nicol 2018; Sabi 2018; Zar 2019). Each study mainly compared the tests head-to-head for the same participants. Xpert Ultra sensitivity (95% CI) was higher (70.5%, 62.7% to 77.45) than that of Xpert MTB/RIF (63.2%, 54.8% to 70.9%), and specificity lower (Xpert Ultra: 97.3%, 95.5% to 98.4% versus Xpert MTB/RIF: 99.2%, 97.8% to 99.7%). The absolute difference in sensitivity was not statistically significant, but test specificity was reduced with Xpert Ultra (P = 0.02) (Table 3).

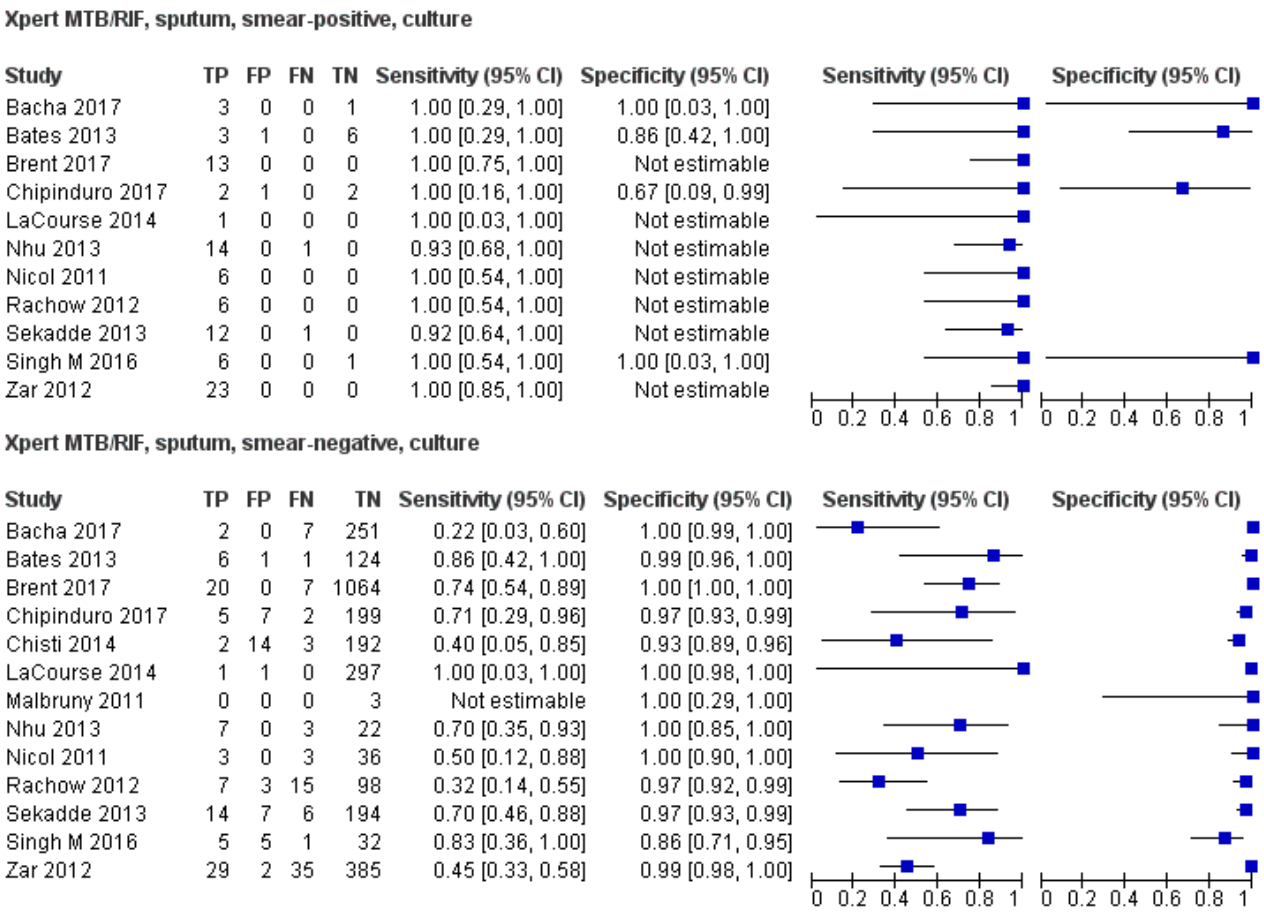
I.D. Investigations of heterogeneity

I.D.1. Xpert MTB/RIF accuracy by smear status

I.D.1.a. Smear-positive

Eleven studies (103 participants) evaluated Xpert MTB/RIF from sputum specimens in smear-positive children against culture (Bacha 2017; Bates 2013; Brent 2017; Chipinduro 2017; LaCourse 2014; Nhu 2013; Nicol 2011; Rachow 2012; Sekadde 2013; Singh M 2016; Zar 2012) (Figure 10). In smear-positive children, Xpert MTB/RIF pooled sensitivity in sputum specimens (95% CI) was 97.8% (91.6% to 99.4%) (Table 2).

Figure 10. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in sputum by smear status (culture reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



I.D.1.b. Smear-negative

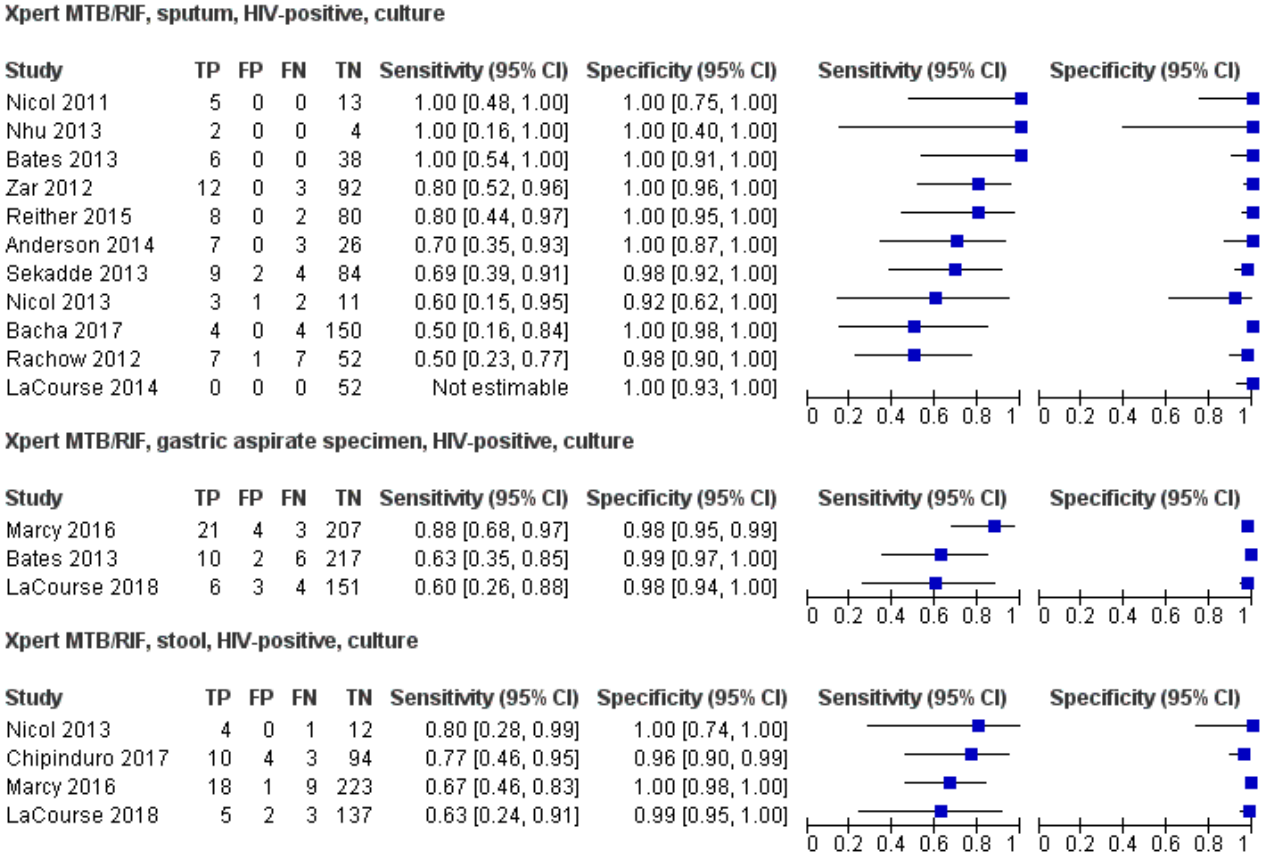
Thirteen studies (3121 participants) evaluated Xpert MTB/RIF from sputum specimens in smear-negative children against culture (Bacha 2017; Bates 2013; Brent 2017; Chipinduro 2017; Chisti 2014; LaCourse 2014; Malbruny 2011; Nhu 2013; Nicol 2011; Rachow 2012; Sekadde 2013; Singh M 2016; Zar 2012) (Figure 10). Malbruny 2011 had no cases of tuberculosis, and so sensitivity was not estimable. For smear-negative children, Xpert MTB/RIF pooled sensitivity and specificity (95% CI) in sputum specimens were 58.9% (45.6% to 71.0%) and 99.1% (97.1% to 99.7%) (Table 2).

I.D.2. Xpert MTB/RIF accuracy by HIV status

I.D.2.a. HIV-positive sputum specimens

In HIV-positive children, 11 studies (649 participants) evaluated Xpert MTB/RIF in sputum specimens (Anderson 2014; Bacha 2017; Bates 2013; Chipinduro 2017; LaCourse 2014; Nhu 2013; Nicol 2011; Nicol 2013; Rachow 2012; Sekadde 2013; Zar 2012) (Figure 11). LaCourse 2014 had no cases of tuberculosis, and so sensitivity was not estimable. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 72.2% (59.9% to 81.8%) and 99.4% (97.2% to 99.9%) (Table 2).

Figure 11. Forest plot of Xpert MTB/RIF sensitivity and specificity in sputum specimens, gastric aspirate specimens, and stool specimens in HIV-positive children (culture reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



I.D.2.b. HIV-negative sputum specimens

In HIV-negative children, 12 studies (Anderson 2014; Bacha 2017; Bates 2013; Bunyasi 2015; LaCourse 2014; Nicol 2011; Nicol 2013; Rachow 2012; Reither 2015; Sekadde 2013; Togun 2015; Zar 2012) (2784 participants) evaluated Xpert MTB/RIF in sputum specimens. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 54.3% (43.5% to 64.7%) and 99.3% (98.1% to 99.7%) (Table 2).

Restricting the analysis to studies that provided data for both HIV-positive and HIV-negative children within the same study did not make a difference in the accuracy estimates.

I.D.2.c. HIV-positive gastric aspirate specimens

In HIV-positive children, three studies (634 participants) evaluated Xpert MTB/RIF in gastric aspirate specimens against culture (Bates 2013; LaCourse 2018; Marcy 2016) (Figure 11). Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 73.3% (54.9% to 86.1%) and 98.5% (97.1% to 99.2%) (Table 2).

I.D.2.d. HIV-positive stool specimens

In HIV-positive children, four studies (526 participants) evaluated Xpert MTB/RIF in stool specimens against culture (Chipinduro 2017; LaCourse 2018; Marcy 2016; Nicol 2013) (Figure 11). Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 69.8% (56.3% to 80.6%) and 98.6% (96.1% to 99.5%) (Table 2).

I.D.3. Xpert MTB/RIF accuracy in children by age group

I.D.3.a. Sputum specimens - induced

In children 5 to 14 years of age, five studies (627 participants) evaluated Xpert MTB/RIF in induced sputum specimens against culture (Chipinduro 2017; Nicol 2011; Rachow 2012; Sekadde 2013; Zar 2012). Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 80.5% (66.9% to 89.4%) and 98.2% (94.4% to 99.4%). In children birth to four years of age, seven studies (2062 participants) evaluated induced sputum specimens against culture (Bunyasi 2015; Chisti 2014; LaCourse 2014; Nicol 2011; Rachow 2012; Sekadde 2013; Zar 2012). Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 48.6% (32.5% to 65.0%) and 99.4% (96.7% to 99.9%). The absolute difference in sensitivity was statistically significant, at 31.9% (95% CI 11.7 to 52.2) (P = 0.002; Table 4).

I.D.3.b. Gastric aspirate specimens

In children birth to four years of age, four studies (1795 participants) evaluated Xpert MTB/RIF in gastric aspirate specimens against

culture. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 43.0% (16.2% to 74.6%) and 99.5% (97.0% to 99.9%) (Table 4).

I.D.4. Xpert MTB/RIF accuracy, effects of tuberculosis burden and TB/HIV burden

I.D.4.a. Countries with high tuberculosis burden

In countries with high tuberculosis burden, 18 studies (5162 participants) evaluated Xpert MTB/RIF in sputum against culture. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 63.8% (53.5% to 73.0%) and 99.1% (97.9% to 99.6%). In countries not considered to be high burden, five studies (1466 participants) evaluated Xpert MTB/RIF in sputum against culture. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 70.2% (46.9% to 86.3%) and 98.8% (97.6% to 99.4%). We did not find a significant difference in accuracy estimates (Table 4).

I.D.4.b. Countries with high TB/HIV burden

In countries with high TB/HIV burden, 19 studies (5824 participants) evaluated Xpert MTB/RIF in sputum against culture. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 65.7% (55.0% to 75.1%) and 99.2% (98.3% to 99.7%). In countries not considered to be high TB/HIV burden, four studies (879 participants) evaluated Xpert MTB/RIF in sputum against culture. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 59.5% (39.6% to 76.7%) and 97.4% (93.8% to 98.9%). We did not find a significant difference in accuracy estimates (Table 5).

I.D.5. Xpert MTB/RIF accuracy in sputum - multiple specimens versus a single specimen used for the reference standard

We stratified studies that inoculated multiple sputum specimens on culture to verify pulmonary tuberculosis (higher-quality reference standard) and those that inoculated a single sputum specimen on culture (lower-quality reference standard) because we suspected that the former was likely to correctly classify more patients with tuberculosis (Figure 6). In comparison to studies that used a single culture (Xpert MTB/RIF pooled sensitivity (95% CI) 69.1% (56.6% to 79.3%) and specificity (95% CI) 98.6% (96.5% to 99.5%)), studies that used multiple cultures had lower sensitivity (95% CI), at 61.0% (48.9% to 71.9%) and similar specificity, at 99.3% (98.4% to 99.7%). We did not find a significant difference in accuracy estimates (Table 4).

II. Detection of tuberculous meningitis

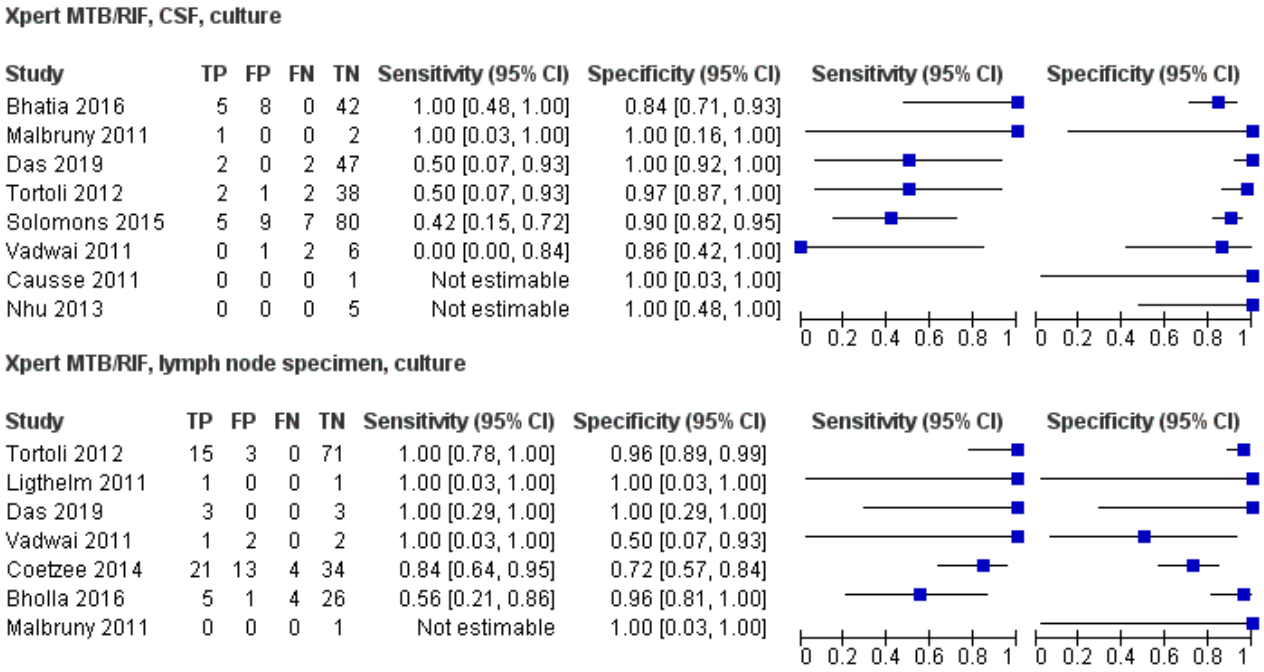
II.A. Xpert MTB/RIF for tuberculous meningitis

Studies were conducted in France, India, Italy, Spain, South Africa, and Vietnam.

II. A.1. Culture reference standard

Eight studies (268 participants) evaluated Xpert MTB/RIF in cerebrospinal fluid against culture (Bhatia 2016; Causse 2011; Das 2019; Malbruny 2011; Nhu 2013; Solomons 2015; Tortoli 2012; Vadwai 2011) (Figure 12). Two of the studies had no cases of tuberculosis, and so sensitivity was not estimable (Causse 2011; Nhu 2013). Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 54.0% (27.8% to 78.2%) and 93.8% (84.5% to 97.6%) (Table 5).

Figure 12. Forest plots of Xpert MTB/RIF sensitivity and specificity for tuberculous meningitis and lymph node tuberculosis (culture reference standard). The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



II.A.2. Composite reference standard

Two studies evaluated Xpert MTB/RIF in cerebrospinal fluid against a composite reference standard. Sensitivities were 25% (95% CI 15 to 39) and 38% (95% CI 22 to 56) (Bhatia 2016; Solomons 2015); specificity was 100% in both studies. We did not perform a meta-analysis owing to insufficient data.

II.B. Xpert Ultra for detection of tuberculous meningitis

We did not identify any studies that evaluated Xpert Ultra for tuberculous meningitis.

III. Detection of lymph node tuberculosis

III.A. Xpert MTB/RIF for detection of lymph node tuberculosis

Studies were conducted in India, Italy, South Africa, and Tanzania.

III.A.1. Culture reference standard

Seven studies (211 participants) evaluated Xpert MTB/RIF in lymph node specimens against culture (Bholla 2016; Coetzee 2014; Das 2019; Ligthelm 2011; Malbruny 2011; Tortoli 2012; Vadwai 2011) (Figure 12). Malbruny 2011 had no cases of tuberculosis, and so sensitivity was not estimable. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 90.4% (55.7% to 98.6%) and 89.8% (71.5% to 96.8%) (Table 5).

III.A.2. Composite reference standard

Three studies (107 participants) evaluated Xpert MTB/RIF in lymph node specimens against a composite reference standard (Bholla 2016; Kim 2015; Ligthelm 2011). Ligthelm 2011 had no cases without tuberculosis, and so specificity was not estimable. In Bholla 2016, Xpert MTB/RIF sensitivity and specificity (95% CI) were 18% (9% to 30%) and 100% (4% to 100%), and in Kim 2015, sensitivity and specificity (95% CI) were 78% (52% to 94%) and 100% (87% to 100%). We did not perform a meta-analysis owing to insufficient data.

III.B. Xpert Ultra for detection of lymph node tuberculosis

We did not identify any studies that evaluated Xpert Ultra for lymph node tuberculosis.

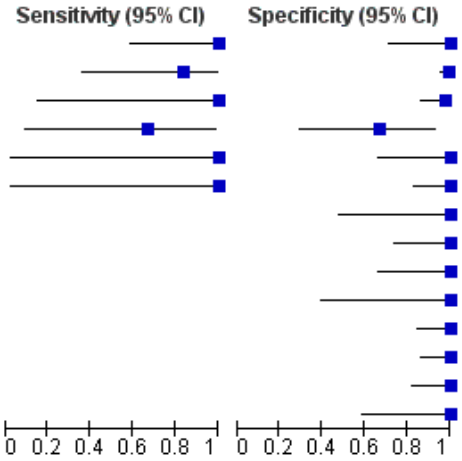
IV. Detection of rifampicin resistance

IV.A. Xpert MTB/RIF for detection of rifampicin resistance

Fourteen studies provided data on detection of rifampicin resistance (Bates 2013; Bholla 2016; Chipinduro 2017; Das 2019; Malbruny 2011; Pang 2014; Rachow 2012; Reither 2015; Saini 2018; Tortoli 2012; Walters 2014; Yin 2014; Zar 2012; Zar 2013) (Figure 13). Studies were conducted in China, India, South Africa, and Zambia. We were able to include only six studies in the meta-analysis because the remaining eight studies did not have any cases of rifampicin resistance, and we could not estimate sensitivity (Bates 2013; Das 2019; Pang 2014; Saini 2018; Yin 2014; Zar 2012). All six studies (223 participants) evaluated only Xpert MTB/RIF and were conducted in countries with high multi-drug-resistant tuberculosis burden. These studies included sputum, gastric and bronchoalveolar lavage, and cerebrospinal fluid and lymph node specimens. Xpert MTB/RIF sensitivity for rifampicin resistance ranged from 67% to 100%, and specificity from 67% to 100%. Xpert MTB/RIF pooled sensitivity and specificity (95% CI) were 90.0% (67.6% to 97.5%) and 98.3% (87.7% to 99.8%) (Table 2).

Figure 13. Forest plots of Xpert MTB/RIF sensitivity and specificity for rifampicin resistance. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Das 2019	7	0	0	11	1.00 [0.59, 1.00]	1.00 [0.72, 1.00]
Zar 2012	5	1	1	114	0.83 [0.36, 1.00]	0.99 [0.95, 1.00]
Bates 2013	2	1	0	38	1.00 [0.16, 1.00]	0.97 [0.87, 1.00]
Saini 2018	2	3	1	6	0.67 [0.09, 0.99]	0.67 [0.30, 0.93]
Pang 2014	1	0	0	9	1.00 [0.03, 1.00]	1.00 [0.66, 1.00]
Yin 2014	1	0	0	20	1.00 [0.03, 1.00]	1.00 [0.83, 1.00]
Bholla 2016	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Malbruny 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Chipinduro 2017	0	0	0	9	Not estimable	1.00 [0.66, 1.00]
Tortoli 2012	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Reither 2015	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Rachow 2012	0	0	0	25	Not estimable	1.00 [0.86, 1.00]
Zar 2013	0	0	0	19	Not estimable	1.00 [0.82, 1.00]
Walters 2014	0	0	0	7	Not estimable	1.00 [0.59, 1.00]



IV.B. Xpert Ultra for detection of rifampicin resistance

We identified one study that evaluated Xpert Ultra in nasopharyngeal specimens for rifampicin resistance verified by MGIT-drug susceptibility testing and MTBDR*plus* as the reference standards (Zar 2019). Of 30 isolates tested, Xpert Ultra identified one isolate as rifampicin-resistant, 22 isolates as rifampicin-susceptible, and seven isolates as inconclusive. Among specimens with valid results, both sensitivity and specificity of Xpert Ultra for detection of rifampicin resistance were 100%.

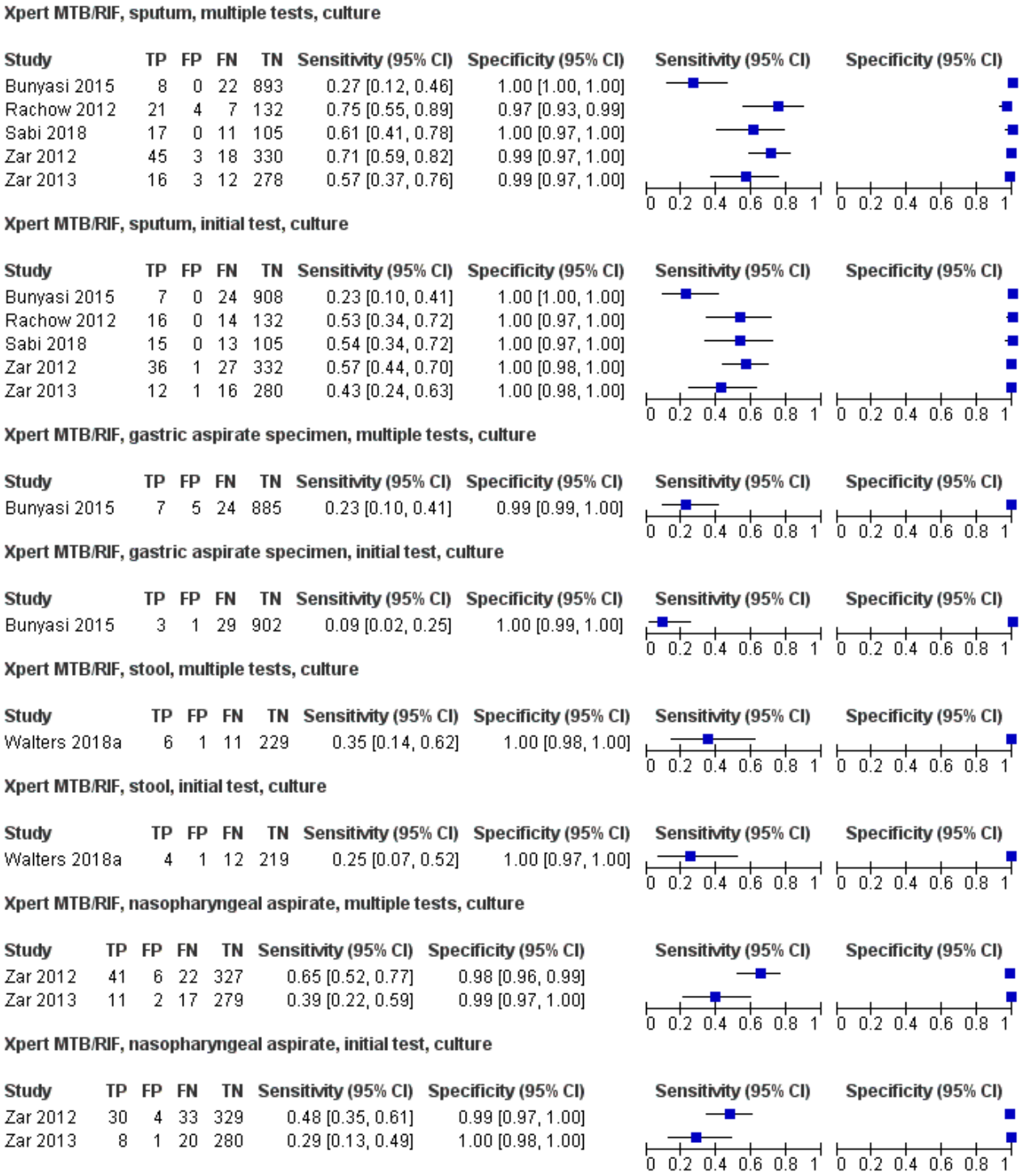
Other analyses

Detection of pulmonary tuberculosis using more than one Xpert MTB/RIF or Xpert Ultra tests

Xpert MTB/RIF

We identified five studies that evaluated more than one Xpert MTB/RIF test (1935 participants) versus a single Xpert MTB/RIF test (1939 participants) in sputum specimens (Bunyasi 2015; Rachow 2012; Sabi 2018; Zar 2012; Zar 2013); one study (935 participants) that evaluated Xpert MTB/RIF in gastric aspirate specimens (Bunyasi 2015); one study (247 participants with multiple Xpert MTB/RIF tests and 236 with one Xpert MTB/RIF test) that evaluated Xpert MTB/RIF in stool specimens (Walters 2018a); and two studies (705 participants) that evaluated Xpert MTB/RIF in nasopharyngeal specimens (Zar 2012; Zar 2013) (Figure 14).

Figure 14. Forest plots of Xpert MTB/RIF sensitivity and specificity for pulmonary tuberculosis in various specimens, multiple Xpert MTB/RIF tests versus one Xpert MTB/RIF test. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



The absolute difference in pooled sensitivity (95% CI) for more than one Xpert MTB/RIF test versus a single Xpert MTB/RIF test by specimen type was 12.8% (-6.78% to 32.3%; P = 0.20) in sputum specimens; 13.2% (-4.64% to 31.1%; P = 0.15) in gastric aspirate

specimens; 13.5% (-9.50% to 36.5%; P = 0.25) in nasopharyngeal specimens; and 10.3% (-20.8% to 41.4%; P = 0.52) in stool specimens. The absolute difference in pooled specificity (95% CI) for multiple Xpert MTB/RIF tests versus a single Xpert MTB/RIF test by specimen type was -0.34% (-1.09% to 0.41%; P = 0.37) for sputum; -0.45% (-0.99% to 0.09%; P = 0.10) for gastric aspirate specimens; -0.49% (-1.63% to 0.66%; P = 0.40) for nasopharyngeal specimens; and 0.02% (-1.21% to 1.25%; P =. 0.97) for stool specimens (Table 6).

Xpert Ultra

We identified one study (135 participants) that evaluated Xpert Ultra in sputum specimens (Sabi 2018), and we identified another study (130 participants) that evaluated Xpert Ultra in nasopharyngeal specimens (Zar 2019) (Figure 8). The absolute difference in pooled sensitivity (95% CI) for more than one Xpert Ultra test versus a single Xpert Ultra test by specimen type was 10.7% (-13.2% to 34.6%; P = 0.38) for sputum specimens and 16.7% (-11.1% to 44.5%; P = 0.25) for nasopharyngeal specimens. The absolute difference in pooled specificity (95% CI) by specimen type was -1.87% (-4.44% to 0.70%; P = 0.16) for sputum and -1.89% (-6.34% to 2.57%; P = 0.41) for nasopharyngeal specimens (Table 6).

Uninterpretable index test results

Detection of tuberculosis, uninterpretable results

Few reported results were uninterpretable (i.e. invalid, error, or no result) for Xpert MTB/RIF and Xpert Ultra for detection of tuberculosis in the included studies. We summarized this information in Table 1.

Indeterminate results, rifampicin resistance

In 15 studies that reported indeterminate results for rifampicin resistance, few Xpert MTB/RIF results were indeterminate for detection of rifampicin resistance. Zero indeterminate results were reported in 11 studies (Bates 2013; Bholla 2016; Das 2019; Gous 2015; Ligthelm 2011; Malbruny 2011; Nhu 2013; Nicol 2011; Rachow 2012; Tortoli 2012; Sekadde 2013). Walters 2018a reported 10% (1/10) indeterminate results in stool specimens, and Zar 2012reported 3% (4/127) indeterminate results in nasopharyngeal and stool specimens.

Sensitivity analyses

We undertook sensitivity analyses by limiting inclusion in the meta-analysis to the following,

- Random or consecutive recruitment of participants.
- Blinding of reference standard to index test results.
- No pre-treatment of participants.
- Enrolment only of children aged 0 to 14 years.
- Sputum only (excluding studies that also collected gastric aspirate specimens).

These sensitivity analyses made little difference to any of the findings (Table 7).

DISCUSSION

Summary of main results

This systematic review summarizes the current literature and includes 49 unique studies on the accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis (TB), tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance. Major findings from the review include the following.

Xpert MTB/RIF accuracy for pulmonary TB (culture reference standard)

- In sputum specimen, Xpert MTB/RIF pooled sensitivity was 64.6% (95% CI 55.3% to 72.9%) (23 studies, 493 participants)
- In gastric aspirate specimens, Xpert MTB/RIF pooled sensitivity was 73.0% (95% CI 52.9% to 86.7%) (14 studies, 273 participants)
- In stool specimens, Xpert MTB/RIF pooled sensitivity was 61.5% (95% CI 44.1% to 76.4%) (11 studies, 174 participants)
- In nasopharyngeal specimens, Xpert MTB/RIF pooled sensitivity was 45.7% (95% CI 27.6% to 65.1%) (4 studies, 144 participants)
- In the above specimens, Xpert MTB/RIF pooled specificity was ≥ 98.1%

Xpert Ultra accuracy for pulmonary tuberculosis (culture reference standard)

- In sputum specimens, Xpert Ultra pooled sensitivity was 72.8% (95% CI 64.7% to 79.6%) (3 studies, 136 participants)
- In nasopharyngeal specimens, Xpert Ultra sensitivity was 45.7% (95% CI 28.9% to 63.3%) (1 study, 35 participants)
- Xpert Ultra specificity was 97.5% in both specimen types

Xpert MTB/RIF accuracy for pulmonary TB (composite reference standard)

- In sputum specimen, Xpert MTB/RIF pooled sensitivity was 19.7% (95% CI 12.1% to 30.4%) (16 studies, 1541 participants)
- In gastric aspirate specimens, Xpert MTB/RIF pooled sensitivity was 31.7% (95% CI 20.2% to 46.0%) (6 studies, 461 participants)
- In stool specimens, Xpert MTB/RIF pooled sensitivity was 16.3% (95% CI 8.4% to 29.2%) (10 studies, 879 participants)
- In the above specimens, Xpert MTB/RIF specificity was ≥ 99.7%

Xpert Ultra accuracy for pulmonary tuberculosis (composite reference standard)

- In sputum specimens, Xpert Ultra sensitivity was 23.5% (95% CI 20.0% to 27.4%) (3 studies, 498 participants)

Xpert MTB/RIF accuracy for tuberculous meningitis (culture reference standard)

- In cerebrospinal fluid, Xpert MTB/RIF sensitivity and specificity were 54.0% (95% CI 27.8% to 78.2%) and 93.8% (95% CI 84.5% to 97.6%) (6 studies, 262 participants; 28 with tuberculosis)

We did not identify any studies of Xpert Ultra for tuberculous meningitis.

Xpert MTB/RIF accuracy for lymph node tuberculosis (culture reference standard)

- In lymph node specimens, Xpert MTB/RIF sensitivity and specificity were 90.4% (95% CI 55.7% to 98.6%) and 89.8% (95% CI 71.5% to 96.8%) (6 studies, 210 participants; 54 with tuberculosis)

We did not identify any studies of Xpert Ultra for lymph node tuberculosis.

Rifampicin resistance

- Xpert MTB/RIF sensitivity and specificity were 90.0% (95% CI 67.6% to 97.5%) and 98.3% (95% CI 87.7% to 99.8%) (6 studies, 223 participants; 20 with rifampicin resistance)

We did not identify studies of Xpert Ultra for detection of rifampicin resistance.

The main findings of the review are summarized in Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4.

Xpert MTB/RIF for pulmonary tuberculosis, sputum specimens

In theory, for a population of 1000 children, 100 of whom have pulmonary tuberculosis on culture, 74 would be Xpert MTB/RIF-positive and 9 (12%) would not have tuberculosis (false-positives); 926 would be Xpert MTB/RIF-negative and 35 (4%) would have tuberculosis (false-negatives) (Summary of findings 1).

Xpert Ultra for pulmonary tuberculosis, sputum specimens

In theory, for a population of 1000 children, 100 of whom have pulmonary tuberculosis on culture, 100 would be Xpert Ultra-positive and 27 (27%) would not have tuberculosis (false-positives); 900 would be Xpert Ultra-negative and 27 (3%) would have tuberculosis (false-negatives) (Summary of findings 1).

Xpert MTB/RIF for tuberculous meningitis, cerebrospinal fluid

In theory, for a population of 1000 children, 100 of whom have tuberculous meningitis on culture, 86 would be Xpert MTB/RIF-positive and 59 (69%) would not have tuberculosis (false-positives); 914 would be Xpert MTB/RIF-negative and 23 (3%) would have tuberculosis (false-negatives) (Summary of findings 2).

Xpert MTB/RIF for lymph node tuberculosis, lymph node specimens

In theory, for a population of 1000 children, 100 of whom have lymph node tuberculosis on culture, 142 would be Xpert MTB/RIF-positive and 97 (68%) would not have lymph node tuberculosis (false-positives); 858 would be Xpert MTB/RIF-negative and 5 (1%) would have lymph node tuberculosis (false-negatives) (Summary of findings 3).

Xpert MTB/RIF for detection of rifampicin resistance

In theory, for a population of 1000 children, 100 of whom have rifampicin resistance, 108 would have Xpert MTB/RIF-rifampicin resistance detected and 18 (17%) would not have rifampicin resistance (false-positives); 892 would have Xpert MTB/RIF-rifampicin resistance NOT detected and 10 (1%) would have rifampicin resistance (false-negatives) (Summary of findings 4).

Overall this review adds to the existing body of evidence on Xpert MTB/RIF and Xpert Ultra diagnostic accuracy in children. Most notable are the new data on performance of different specimen types that are now being introduced to improve access to diagnostic testing for tuberculosis in children. Further, this review expands on evidence supporting the increase in test sensitivity that is achieved through testing multiple specimens by Xpert MTB/RIF and Xpert Ultra. These findings provide new evidence by which to shape the development of global practice guidelines for the diagnosis of tuberculosis in children.

Specifically, our review demonstrated differing sensitivities in the different types of specimens. We think that these findings may in part be attributable to differences in the clinical setting and in the quality of the reference standard, mainly culture. With respect to the clinical setting, it is more common to collect gastric aspirate specimens in inpatient settings; further, these settings tend to include a higher number of children with advanced disease, which often has a higher microbiological yield (Marais 2006d). Thus, the higher sensitivity against a culture and composite reference standard for gastric aspirate specimens may in part be due to the inpatient setting and higher likelihood of advanced disease. Regarding the reference standard, some studies performed only one culture, and other studies more than one culture, to verify tuberculosis. We considered multiple cultures to be a higher-quality reference standard. However, we did not observe a significant difference in Xpert MTB/RIF accuracy in sputum when multiple versus single cultures were used to verify pulmonary tuberculosis. In some studies from low-income countries, only one culture was performed; this is consistent with standard practice in many countries with a high burden of tuberculosis. As has been previously documented, the sensitivity (95% CI) of Xpert MTB/RIF was nearly perfect in children with smear-positive tuberculosis 97.8% (91.6% to 99.4%) and was still 58.9% (45.6% to 71.0%) in the smear-negative subgroup. Data indicate clearly that the diagnostic accuracy of Xpert MTB/RIF is superior to that of sputum smear in children.

Against a composite reference standard, we found that Xpert MTB/RIF had a sensitivity of 19.7% and Xpert Ultra had a sensitivity of 23.5%. These results were higher then those reported in the prior review (Detjen 2015) and may reflect changes in the consensus definition or the broader sample of research sites included in this review. In adults, Xpert Ultra trace results may be more likely to reflect false-positive results, particularly in patients with prior tuberculosis (Dorman 2018). Xpert Ultra trace results on sputum were reported in two studies (Nicol 2018; Sabi 2018). Twenty-one trace results were obtained on frozen specimens, with 20 occurring in patients with confirmed or unconfirmed tuberculosis; one occurred in a patient with unlikely tuberculosis. Nasopharyngeal specimens specifically yielded nine trace results (Zar 2019), none of which were identified in patients unlikely to have tuberculosis. These limited data suggest that trace results in children indicate true disease and should be treated as such. More data are needed with regard to trace results, particularly on specimens other than sputum.

We found the sensitivity (95% CI) of stool Xpert MTB/RIF to be slightly lower at 61.5% (44.1% to 76.4%) than that of sputum Xpert MTB/RIF at 64.6% (95% CI 55.3% to 72.9%). Nonetheless, stool is a promising specimen for diagnosis because, unlike sputum, it is non-invasive. Its greatest benefit may be seen in children younger than five years owing to the challenges of collecting specimens through sputum induction and gastric aspiration in this population. However, no studies evaluating Xpert MTB/RIF in stool provided disaggregated data for analyses in the youngest age groups. As in MacLean 2019, we noted the lack of standardized procedures for processing stool, with each study using a different approach.

When multiple specimens of the same type were tested, we noted an increase in Xpert MTB/RIF sensitivity for pulmonary tuberculosis in all specimen types. In comparison with testing

an initial specimen, Xpert MTB/RIF specificity was similar when multiple specimens were tested.

In a head-to-head comparison of frozen sputum specimens, Xpert Ultra yielded higher sensitivity (70.5%) than Xpert MTB/RIF (63.2%) and lower specificity (Ultra: 97.3% versus Xpert MTB/RIF: 99.2%). Although in comparison with Xpert MTB/RIF, Ultra specificity was slightly decreased, the improvement in Xpert Ultra sensitivity may provide greater benefit than the harm associated with a slight reduction in Ultra specificity in the paediatric population.

In subgroup analyses, we found the sensitivity of Xpert MTB/RIF to be higher in HIV-positive than HIV-negative children. These findings were similar when we limited the analysis to studies that included both HIV-positive and HIV-negative children in the same study. We note that the number of cases in most studies was small: HIV-positive group, median (interquartile range) = 8 (5 to 13), and HIV-negative group, median (interquartile range) = 13 (5.5 to 26). We think random variation may in part explain these results, although they may also reflect the increased likelihood of presentation with severe tuberculosis in HIV-positive children.

Regarding age, we found higher sensitivity of Xpert MTB/RIF in sputum from children 5 to 14 years old compared to children 0 to 4 years old. The sensitivity of Xpert MTB/RIF in gastric aspirate specimens from children 0 to 4 years old was similar to that in sputum. This has implications for clinical decision-making in children 0 to 4 years of age, when a negative Xpert may provide less reassurance to the treating clinician, particularly due to higher risk for adverse tuberculosis outcomes in this population.

Although Xpert MTB/RIF sensitivity in lymph node specimens was 90%, specificity was lower than in sputum specimens (98%). Regarding the accuracy of the reference standard in lymph node specimens in particular, several factors may have contributed to false-negative culture results, including inefficient specimen collection and overly harsh decontamination (Kohli 2018). As with pulmonary tuberculosis, the sensitivity of Xpert MTB/RIF for tuberculous meningitis is not adequate to withhold treatment based on the test result, and the entirety of the clinical information must be considered.

For detection of rifampicin resistance, we found Xpert MTB/RIF to have lower sensitivity (95% CI) at 90.0% (67.6% to 97.5%) than that in a Cochrane Review of Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults at 96% (94% to 97%) (Horne 2019). We note that in the current review, only 20 rifampicin-resistant specimens contributed to the determination of sensitivity, whereas in Horne 2019, there were 1775 rifampicin-resistant specimens. Compared to the current review, the sensitivity estimate in Horne 2019 was more precise. Specificities were similar (98%).

We identified one large pilot project in India that evaluated Xpert MTB/RIF for pulmonary tuberculosis in sputum verified by smear microscopy (Raizada 2015a). We did not include this study in our systematic review because the reference standard (smear) did not satisfy the criterion for inclusion. Results of this project demonstrated high sensitivity (1521/1530; 99.4%) of Xpert MTB/RIF against smear.

Strengths and weaknesses of the review

Completeness of evidence

The data set resulted from comprehensively searching numerous databases, handsearching references of included studies, and contacting investigators for additional evidence. We included all identified non-English studies from which we could obtain accuracy data. However, we acknowledge that we may have missed some studies despite the comprehensive search and outreach to investigators. We included the two most common forms of extrapulmonary tuberculosis - tuberculous meningitis and lymph node tuberculosis. Hence, the review does not include an evaluation of the accuracy of Xpert MTB/RIF and Xpert Ultra in less common forms of child tuberculosis.

Accuracy of the reference standards used

In a systematic review of diagnostic test accuracy studies, the reference standard is the best available test to determine the presence or absence of the target condition. In this review, we included two reference standards - culture and a composite reference standard. Although culture is the best available microbiological reference standard, it is not a perfect reference standard for active tuberculosis in children owing to the paucibacillary nature of the disease. Some studies performed only one culture and others more than one culture to verify tuberculosis. We considered multiple cultures to be a higher-quality reference standard. We also evaluated the accuracy of Xpert MTB/RIF and Xpert Ultra against a composite reference standard defined as (1) a positive culture or a clinician decision to treat for pulmonary or extrapulmonary tuberculosis, or (2) a standardized research definition of child tuberculosis. The accuracy of composite reference standards is also variable and limited (in most analyses, Xpert MTB/RIF and Ultra identified less than 30% of cases) but may reflect the paucibacillary nature of childhood tuberculosis, which is not taken into account when culture positivity is taken as the reference standard for comparison. If data on tuberculosis treatment were not provided, we accepted the uniform research definitions or the definition used by the primary study authors (study-specific definition) for the composite reference standard. Therefore, clinical characteristics and component tests in the composite reference standard differed across studies, and these differences may have contributed to variation in accuracy estimates.

Quality of reporting of the included studies

We considered risk of bias to be low for the patient selection, index test, and flow and timing domains, and low or unclear for the reference standard domain, because some studies collected only a single specimen for culture. In general, studies were fairly well reported. When data were unclear, or when we needed additional information, we corresponded with many of the primary study authors. The quality of the studies was good, but for some specimen types and for Xpert Ultra, the numbers of studies and participants enrolled were small, limiting our ability to draw definitive conclusions in these circumstances.

Comparison with other systematic reviews

Our systematic review on the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for tuberculosis in children builds on a prior systematic review on this topic - Detjen 2015 - and includes 34 additional studies on Xpert MTB/RIF published since that time, as

well as emerging data on Xpert Ultra. For detection of pulmonary tuberculosis, Detjen 2015 found Xpert MTB/RIF sensitivity of 62% in sputum specimens and 66% in gastric aspirate specimens against culture. The current review found slightly higher Xpert MTB/RIF sensitivity estimates - 65% in sputum specimens and 73% in gastric aspirate specimens. Another systematic review for pulmonary tuberculosis found Xpert MTB/RIF sensitivity of 65% in respiratory specimens (culture reference standard) (Wang 2015) - similar to the pooled sensitivity estimate for sputum specimens in this review. Specificity in these reviews was similar to ours, at 98% to 99%.

We identified two additional systematic reviews on the diagnostic accuracy of Xpert MTB/RIF in stool specimens. MacLean 2019 found that stool Xpert MTB/RIF had a pooled sensitivity of 67% against a microbiological reference standard consisting of either culture or Xpert MTB/RIF on a respiratory specimen. Mesman 2019 found that stool Xpert MTB/RIF had a pooled sensitivity of 57% against culture on respiratory specimens and 60% against Xpert MTB/RIF on respiratory specimens. Our systematic review found stool Xpert MTB/RIF had a pooled sensitivity of 61.5% against a microbiological reference standard consisting of either culture or Xpert MTB/RIF on respiratory specimens - findings consistent with those of the prior reviews. Specificity in both reviews was similar to ours, at 98% to 99%.

Applicability of findings to the review question

To assess the applicability of findings to the review question, we considered QUADAS-2 domains for patient selection, index test, and reference standard. With respect to the patient selection domain, we considered many studies to have high or unclear risk of bias because either patients were evaluated exclusively as inpatients in a tertiary care setting or the clinical setting was not clearly reported. Therefore, our findings cannot definitively be applied to the primary care setting. Studies that take place in referral settings may include patients whose condition is more advanced or more difficult to diagnose than patients seen at lower levels of the health system. With respect to the index test, we considered most studies to have low concern about applicability. However, we considered applicability of the index test in stool to be unclear, as currently, there is not a standardized protocol for stool testing with Xpert MTB/RIF or Xpert Ultra. The applicability of Xpert Ultra in respiratory specimens comes with some uncertainty, as all data were reported in frozen specimens. With respect to the reference test domain, we considered most studies to have low concern about applicability.

AUTHORS' CONCLUSIONS

Implications for practice

For detection of pulmonary tuberculosis, the sensitivity of Xpert Ultra was higher than that of Xpert MTB/RIF in sputum, suggesting that Xpert Ultra may detect an increased proportion of paucibacillary tuberculosis in children. Although in comparison with Xpert MTB/RIF, Ultra specificity was slightly decreased, the improvement in Xpert Ultra sensitivity may provide greater benefit than the harm associated with a slight reduction in Ultra specificity in the paediatric population. Nonetheless, owing to the small numbers of studies and participants in many of the analyses in this review, we advise caution in interpreting these results. In addition, we note that, in this review, all studies assessing the performance of Xpert Ultra evaluated the test in frozen specimens originally collected for testing Xpert MTB/RIF. Additional prospective studies on the performance of Xpert Ultra in fresh clinical specimens are needed. As always, the prevalence of tuberculosis in the test population will influence the predictive value of Xpert MTB/RIF and Xpert Ultra results.

Xpert MTB/RIF sensitivity (defined by culture) for pulmonary tuberculosis was variable across different specimen types, including sputum, gastric, stool, and nasopharyngeal specimens. The highest sensitivity was seen with gastric aspirate specimens, followed by sputum specimens, and the lowest in nasopharyngeal specimens. Specificity was high in all of these aforementioned specimens. Xpert MTB/RIF sensitivity may increase when multiple specimens of the same type are tested compared with a single specimen. Although not evaluated in this review, it is likely that collecting multiple specimens of different types will also increase Xpert MTB/RIF and Xpert Ultra sensitivity. However, considering the difficulties of collecting sputum specimens from children, as well as the limitations of culture to verify the diagnosis of tuberculosis, clinicians should consider collecting additional specimens, whenever possible the least invasive, for testing with Xpert MTB/RIF or Xpert Ultra. The lower sensitivity of the Xpert MTB/RIF test in children 0 to 4 years of age should prompt clinicians not only to collect multiple specimens but also to treat based on other clinical information in this vulnerable population.

Xpert MTB/RIF was accurate for detection of rifampicin resistance.

Xpert MTB/RIF was sensitive for lymph node tuberculosis. Regarding tuberculous meningitis, as with pulmonary tuberculosis, treatment decisions should be based on the entirety of clinical information, and treatment not withheld based solely on an Xpert MTB/RIF result.

Evidence in this review is based mainly on culture as the reference standard and accuracy calculated on the assumption that the reference standard is 100% sensitive and specific. Although culture is acceptable, it is an imperfect reference standard for child tuberculosis. Without a more accurate reference standard that has a limit of detection low enough to detect paucibacillary tuberculosis, the accuracy of novel diagnostic tests for tuberculosis in children will remain difficult to estimate. Despite the presence of a negative Xpert MTB/RIF or Xpert Ultra result, clinicians will still need to consider anti-tuberculosis treatment in children with a high suspicion of tuberculosis or at high risk of a poor outcome.

Implications for research

There are several areas for which additional research regarding the diagnostic accuracy of molecular tests in children is necessary. Studies are urgently needed that evaluate the accuracy of Xpert Ultra in gastric and stool specimens for pulmonary tuberculosis and extrapulmonary tuberculosis in children. Ideally, these studies would be prospective and would evaluate fresh specimens, rather than retrospective utilizing frozen specimens. Establishing the diagnostic accuracy of Xpert Ultra in extrapulmonary specimens is also an urgent need, particularly given the encouraging results regarding Xpert Ultra performance in cerebrospinal fluid obtained from adults.

Xpert MTB/RIF sensitivity estimates increased with multiple as compared to one specimen in a small number of studies; however, additional studies evaluating the combinatorial benefit

of multiple specimen types are needed. Limited data suggest that the combination of non-invasive specimens performs comparably with traditional gastric aspirate specimens or induced sputum specimens.

More research is needed to identify an improved reference standard that accurately defines tuberculosis in children. Additional operational and qualitative research is needed to determine the best approach to less invasive specimen collection. Implementation studies on a method of suction for nasopharyngeal aspiration that is appropriate for low-skill or low-resource environments are needed. Addtional operational research concerning the use of stool as a diagnostic specimen is needed. These studies should address integration into normal diagnostic clinical pathways, definition of laboratory protocols that successfully balance ease of implementation and diagnostic performance, and the impact of stool testing on patient-important outcomes. There is a dearth of qualitative research identifying child and family preferences for and acceptability of comparative diagnostic approaches and specimen collection procedures.

We underscore the continued urgent need to develop new tools that accurately diagnose tuberculosis in children. Ideally, these new tools will be rapid, affordable, feasible, and acceptable to children and their parents.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anderson 2014

Study characteristics	
Patient Sampling	Cohort study, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: persistent cough for > 2 weeks; pneumonia not responding to first-line antibiotics; unexplained fever for > 2 weeks; unexplained progressive weight loss or failure to thrive for > 4 weeks; history of close TB contact; and/or a doctor's clinical suspicion of TB for any other reason. Children with ≥ 1 of these features plus those referred for outpatient investigation for TB and children < 5 years old who were identified as household TB contacts of smear-positive pulmonary TB were eligible for inclusion in the study Age: range for study population 0 to 180 months; culture-confirmed cases: median (interquartile range) 37 (12 to 104) months Sex, female: 35% HIV infection: 40% Sample size included for analysis: 134 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: not reported Country: Kenya World Bank income classification: middle income

Anderson 2014 *(Continued)*

	High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 26%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard (received tuberculosis treatment)
Flow and timing	87% of enrolled children were excluded before selection for the array study for feasibility
Comparative	
Notes	Primary aim of study was to evaluate a gene signature for TB diagnosis

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Anderson 2014 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Andriyoko 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: presumptive TB symptoms (no additional details) Age: median (IQR) 17 (5.5 to 78) months Sex: NR HIV infection: NR Sample size included for analysis: 27 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: Indonesia World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 22%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Xpert test on standard specimens (7 induced sputum and 20 gastric specimens)
Flow and timing	Index and reference test specimens were collected within 7 days
Comparative	
Notes	No consensus has been reached on appropriate stool processing methods; this study used gravity separation
Methodological quality	

Andriyoko 2019 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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	

Atwebembeire 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: presumptive TB symptoms (no additional details) Age: 18% younger than 60 months; 82% 60 months or older Sex, female: 55% HIV infection: 31% Sample size included for analysis: 85 Clinical setting: inpatient Laboratory level where index test was performed: research Country: Uganda World Bank income classification: low income High TB burden country: no High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 13%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; LJ
Flow and timing	Index and reference test specimens were collected within 7 days of each other
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		
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	

Atwebembeire 2016 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
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	

Bacha 2017

Study characteristics	
Patient Sampling	Cohort, consecutive, retrospective
Patient characteristics and setting	Presenting signs and symptoms: clinicians used a combination of TB screening questions (e.g. history of known TB contact, failure to gain weight/weight loss, persistent cough, persistent fever, reduced activities, irritability) and clinical examination findings (e.g. malnutrition, lymphadenopathy, abnormal lung findings) based on national guidelines Age: mean (range) 60 (1 to 168) months Sex, female: 52% HIV infection: 54% Sample size included for analysis: 286 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: research Country: Tanzania World Bank income classification: low income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 13%

Bacha 2017 *(Continued)*

Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Microbiological confirmation (culture type not reported); composite reference standard; clinical reference standard (received tuberculosis treatment)
Flow and timing	Xpert and reference test performed within 7 days of each other
Comparative	
Notes	All patients did not have a specimen collected for the microbiological reference standard

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	

Bacha 2017 *(Continued)*

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?	No	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		High risk

Bates 2013

Study characteristics	
Patient Sampling	Cross-sectional design, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: suspected tuberculosis defined as having tuberculosis on the basis of a symptom-and-risk factor screen (≥ 1 of 5 factors: cough for longer than 2 weeks, weight loss, malnutrition, HIV, or tuberculosis contact) according to the Zambia National TB Programme and WHO guidelines Age: median (IQR) 24 (12 to 74) months Sex, female: not reported HIV infection: 32% Sample size included for analysis: 142 for expectorated sputum; 788 for gastric aspirate lavage Clinical setting: inpatient Laboratory level where index test was performed: university hospital laboratory (tertiary referral centre) Country: Zambia World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of TB cases in the study: 5%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Target condition: pulmonary tuberculosis Reference standard: MGIT
Flow and timing	Index and reference tests were collected simultaneously
Comparative	

Bates 2013 *(Continued)*

Notes	Only 1 culture was used to exclude TB, indicating an unclear ability of the reference standard to classify the target condition

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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		

Bates 2013 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Bhatia 2016

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: clinically suspected TBM (fever > 1 week, headache, vomiting, neck stiffness, convulsions, focal deficits, altered consciousness, history of TB contact) Age: median 59 months Sex, female: 41% HIV infection: not reported Sample size included for analysis: 55 Clinical setting: inpatient Laboratory level where index test was performed: regional Country: India World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 10%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Tuberculous meningitis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index test and reference standard were collected simultaneously
Comparative	
Notes	Only 1 culture was used to exclude TB, indicating an unclear ability of the reference standard to classify the target condition

Methodological quality

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

Bhatia 2016 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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	

Bholla 2016

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: ≥ 1 palpable lymph nodes ≥ 1 cm persisting for longer than 4 weeks in spite of oral antibiotic therapy and a strong clinical suspicion or microbiological confirmation of mycobacterial infection Age: 0 to 60 months (59%); 61 to 204 months (41%) Sex, female: 39% HIV infection: 20% Sample size included for analysis: 75 Clinical setting: not reported Laboratory level where index test was performed: not reported Country: Tanzania World Bank income classification: low income

Bholla 2016 *(Continued)*

	High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 9%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Lymph node tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests performed simultaneously
Comparative	
Notes	There was a high percentage of culture contamination (48%), and only 1 culture was used to exclude TB, indicating an unclear ability of the reference standard to classify the target condition

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Bholla 2016 *(Continued)*

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

Brent 2017

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children aged < 15 years were investigated for TB if ≥ 1 of the following features of suspected TB were present and they were not already on TB treatment; unexplained persistent cough for > 2 weeks; pneumonia not responding to first-line antibiotics; unexplained fever for > 2 weeks; unexplained progressive weight loss or failure to thrive for > 4 weeks; history of close contact with a suspected or confirmed case of pulmonary TB; clinical suspicion of TB for any other reason Age, months: confirmed group median (IQR) 53 (21 to 112) Sex, female: confirmed group 39% HIV infection: confirmed group 28% Sample size included for analysis: 1442 Clinical setting: not reported Laboratory level where index test was performed: not reported Country: Kenya World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 4%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected simultaneously
Comparative	
Notes	

Brent 2017 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
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	

Bunyasi 2015

Study characteristics	
Patient Sampling	Randomized controlled trial, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children were followed quarterly for ≥ 2 years to identify signs, symptoms, or household exposure that merited investigation for suspected TB disease, for example, weight loss in the preceding 2 months, cough for longer than 2 weeks without improvement, failure to thrive, conversion to a positive test of TB infection Age, months: median (IQR) 16.8 (12.0 to 22.1) Sex, female: 54% HIV infection: 0% Sample size included for analysis: 1020 Clinical setting: inpatient Laboratory level where index test was performed: not reported Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 3%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT
Flow and timing	Index test and reference standard were collected simultaneously
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Bunyasi 2015 *(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)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Causse 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: presumptive tuberculosis Age, months: mean 43 Sex, female: not reported HIV infection: 0% Sample size included for analysis: 44 Clinical setting: not reported Laboratory level where index test was performed: central Country: Spain World Bank income classification: high income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: not reported

Causse 2011 *(Continued)*

Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary TB; tuberculous meningitis Liquid culture (Middlebrook)
Flow and timing	Index and reference tests were collected simultaneously
Comparative	
Notes	It is unclear whether those interpreting the reference test were blinded to results of the index test

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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

Causse 2011 *(Continued)*

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

Chipinduro 2017

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, unknown
Patient characteristics and setting	Presenting signs and symptoms: participants were children 5 to 16 years of age presenting with a chronic cough of 2 weeks and any of the classic signs and symptoms of TB, including weight loss, loss of appetite, persistent fever without an apparent cause, night sweats, or history of close contact with a TB index patient, defined as living in close proximity (sharing a room within a household) with an adult diagnosed with TB within the preceding 12 months Age, months: median 127 Sex, female: 56% HIV infection: 50% Sample size included for analysis: 218 Clinical setting: outpatient Laboratory level where index test was performed: not reported Country: Zimbabwe World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 9%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid culture (LJ); composite reference standard; clinical reference standard
Flow and timing	Index test and reference standard were collected within pre-specified interval
Comparative	
Notes	Study evaluated Xpert MTB/RIF in stool and induced sputum; no consensus has been reached on the proper stool processing method for Xpert; this study used centrifugation
Methodological quality	

Chipinduro 2017 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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	

Chisti 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: respiratory symptoms (cough and/or respiratory distress) and radiological pneumonia Age, months: mean 12 Sex, female: not reported HIV infection: not reported Sample size included for analysis: 214 Clinical setting: inpatient Laboratory level where index test was performed: research laboratory Country: Bangladesh World Bank income classification: low income High TB burden country: yes High TB/HIV burden country: no High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 5%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid culture (LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
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		

Chisti 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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	

Coetzee 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: all children < 13 years of age who were referred to the fine needle aspirate clinics or were admitted to the inpatient wards/clinics of both hospitals with persistent superficial lymphadenopathy and clinical suspicion of mycobacterial infection were included in the study Age, months: median 23 Sex, female: 40% HIV infection: 8% Sample size included for analysis: 72 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes

Coetzee 2014 *(Continued)*

	Prevalence of tuberculosis cases in the study: 35%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Lymph node TB MGIT
Flow and timing	Index and reference tests were collected within pre-specified time
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	

Coetzee 2014 *(Continued)*

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

Das 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: ≥ 1 of the following symptoms persisting for > 2 weeks without sustained improvement or resolution following appropriate treatment for other potential diagnoses (e.g. antibiotics for pneumonia; antimalarials for fever; nutritional support for failure to thrive): cough, fever, weight loss, or failure to thrive. Signs and symptoms of meningitis not responding to antibiotic treatment, with a subacute onset and/or raised intracranial pressure. Non-painful enlarged lymph nodes without fistula formation Age, months: 45% 0 to 60, 55% 61 to 180 Sex, female: 40% HIV infection: 2% Sample size included for analysis: 171 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: university hospital laboratory Country: India World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 10%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis; lymph node tuberculosis; tuberculosis meningitis Solid culture (LJ)
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	

Das 2019 *(Continued)*

Methodological quality

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

Gous 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: clinician suspicion of pulmonary tuberculosis Age, months: median 24 Sex, female: not reported HIV infection: not reported Sample size included for analysis: 345 Clinical setting: not reported Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 4%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	Children younger than 5 years had small volumes of sputum collected via physiotherapy-supported expectoration; Xpert was performed after "top up" of these small volumes with normal saline

Methodological quality

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

Gous 2015 *(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?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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	

Hanrahan 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: inclusion criteria for presumptive tuberculosis: (i) children 60 days to ≤ 10 years of age were eligible if they presented with ≥ 1 signs and symptoms of presumptive TB: persistent, non-remitting, and unexplained cough for ≥ 2 weeks; (ii) unexplained weight loss > 5% in the last 3 months or failure to thrive, and not responding to nutritional rehabilitation (or antiretroviral treatment if HIV-positive); (iii) persistent and unexplained fever for 1 week or longer; persistent, unexplained lethargy or decrease in playfulness/activity. Symptomatic child household contacts of an adult diagnosed with TB were also offered participation in the study regardless of symptom duration Age, months: median (IQR) 21.4 (12 to 43) Sex, female: 47% HIV infection: 18% Sample size included for analysis: 99 Clinical setting: outpatient Laboratory level where index test was performed: Central Country: South Africa

Hanrahan 2018 *(Continued)*

	World Bank income classification: Upper middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 3%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	Stool was included as a specimen for index testing; no protocol has been established for stool processing; the approach used in this study was centrifugation; method used for confirmation of *M tuberculosis* by culture was not reported

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Hanrahan 2018 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			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	

Hasan 2017

Study characteristics	
Patient Sampling	Cross-sectional, convenience, prospective
Patient characteristics and setting	Presenting signs and symptoms: children younger than 15 years based on clinical symptoms, chest radiography, and Kenneth Jones score ≥ 5 Age, months: median (IQR) 82 (24 to 108) Sex, female: 22% HIV infection: 0% Sample size included for analysis: 50 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: intermediate Country: Pakistan World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: no High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 18%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	

Hasan 2017 *(Continued)*

Notes	The index test was performed on stool; no stool processing method for Xpert has been established; centrifugation was used in this study

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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		

Hasan 2017 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Kasa Tom 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children younger than 15 years with presumptive TB symptoms Age, months: median (IQR) 36 (17 to 72) Sex, female: 35% HIV infection: 18% Sample size included for analysis: 93 Clinical setting: inpatient Laboratory level where index test was performed: central Country: Papa New Guinea World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 95% composite
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Composite reference standard
Flow and timing	Index and reference data were collected within pre-specified time period
Comparative	
Notes	Only some children received the microbiological reference standard, so only a composite reference standard was applied

Methodological quality

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

Kasa Tom 2018 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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?			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?	No		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		High risk	

Kim 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, retrospective
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 18 years of age evaluated for extrapulmonary tuberculosis in whom Xpert MTB/RIF was used, as well as culture, and who were not on treatment for tuberculosis Age, months: not reported Sex, female: not reported HIV infection: not reported Sample size included for analysis: 30 Clinical setting: inpatient Laboratory level where index test was performed: regional Country: South Korea World Bank income classification: high income

Kim 2015 *(Continued)*

	High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 13%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Lymph node tuberculosis Composite reference standard		
Flow and timing	Index and reference tests were performed within pre-specified time period		
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Kim 2015 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

LaCourse 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: enrollees met WHO severe acute malnutrition criteria for children aged 6 to 60 months with weight-for-height z-score ≤ 3 standard deviations below the median, mid-upper arm circumference (MUAC) ≤ 115 mm, or bilateral pedal oedema Age, months: median (IQR0 18 (12 to 26) Sex, female: 51% HIV infection: 18% Sample size included for analysis: 300 Clinical setting: inpatient Laboratory level where index test was performed: research Country: Malawi World Bank income classification: low income High TB burden country: no High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 0.6%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	
Methodological quality	

LaCourse 2014 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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?	No		
If a threshold was used, was it pre-specified?	No		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

LaCourse 2018

Study characteristics	
Patient Sampling	Randomized controlled trial, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: all children living with HIV who were hospitalized with an acute illness Age, months: median (IQR) 24 (13 to 58) Sex, female: 45% HIV infection: 100% Sample size included for analysis: 165 Clinical setting: inpatient Laboratory level where index test was performed: central Country: Kenya World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 6%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	No protocol for stool processing has been established; this study used the centrifugation method in a central laboratory

Methodological quality

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

LaCourse 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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ligthelm 2011

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age, months: mean 36 Sex, female: not reported HIV infection: not reported Sample size included for analysis: 50 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: central Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 60%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Lymph node tuberculosis

Ligthelm 2011 *(Continued)*

	MGIT; composite reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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?	Unclear		
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		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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			

Ligthelm 2011 *(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	

Malbruny 2011

Study characteristics			
Patient Sampling	Cross-sectional, manner of selection not reported, prospective		
Patient characteristics and setting	Presenting signs and symptoms: clinically suspected tuberculosis Age, months: mean 88 Sex, female: not reported HIV infection: not reported Sample size included for analysis: 12 Clinical setting: laboratory Laboratory level where index test was performed: research laboratory Country: France World Bank income classification: high income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 8%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Pulmonary TB, lymph node TB, tuberculous meningitis Solid culture; composite reference standard		
Flow and timing	Index and reference tests were collected within pre-specified time period		
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?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	

Malbruny 2011 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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	

Marcy 2016

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children aged ≤ 13 years with suspicion of intrathoracic tuberculosis based on ≥ 1 of the following: persistent cough; persistent fever; failure to thrive, defined as recent deviation in the growth curve or weight-for-age z-score < −2 standard deviations; failure of broad-spectrum antibiotics for pulmonary infection; suggestive chest radiograph anomaly

Marcy 2016 *(Continued)*

	Age, months: median (IQR) 86 (49 to 85) Sex, female: 49% HIV infection: 100% Sample size included for analysis: 272 Clinical setting: not reported Laboratory level where index test was performed: not reported Country: Burkina Faso; Cambodia; Cameroon; Vietnam World Bank income classification: low and middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 11%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT and LJ; composite reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	No method for stool processing with Xpert has been established; this study used centrifugation

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			

Marcy 2016 *(Continued)*

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

Moussa 2016

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children older than 1 year and younger than 15 years with clinical signs of PTB Age, months: not reported Sex, female: 39% HIV infection: 0% Sample size included for analysis: 115 Clinical setting: not reported Laboratory level where index test was performed: intermediate Country: Egypt World Bank income classification: middle income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 31%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid culture (LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period

Moussa 2016 *(Continued)*

Comparative	
Notes	No method for stool processing before Xpert has been established; this study used centrifugation

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
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		
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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Moussa 2016 *(Continued)*

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Myo 2018

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 13 years of age or younger with suspected PTB were recruited into the study. PTB was suspected if a child had cough for ≥ 14 days and any of the following features; fever for 7 days, failure to thrive, unexplained loss of appetite, or lethargy Age, months: median 48 Sex, female: 47% HIV infection: 13% Sample size included for analysis: 231 Clinical setting: inpatient Laboratory level where index test was performed: central Country: Myanmar World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 7%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid culture (LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference test specimens were collected within prespecified time period
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?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Myo 2018 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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	

Nhu 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: clinical suspicion of tuberculosis Age, months: median 106 Sex, female: not reported HIV infection: 10% Sample size included for analysis: 72 Clinical setting: inpatient

Nhu 2013 *(Continued)*

	Laboratory level where index test was performed: intermediate Country: Vietnam World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: no High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 30%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis and tuberculous meningitis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Nhu 2013 *(Continued)*

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

Nicol 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: cough for longer than 14 days and 1 of the following: household contact infected with tuberculosis within previous 3 months, loss of weight or failure to gain weight in previous 3 months, positive skin test to purified protein derivative, or chest radiograph suggestive of pulmonary tuberculosis Age, months: median 72 Sex, female: not reported HIV infection: 37% Sample size included for analysis: 48 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 15%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	

Nicol 2011 *(Continued)*

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

Nicol 2013

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 14 years of age with cough lasting longer than 2 weeks and at least 1 of the following: (1) household tuberculosis contact in prior 3 months, (2) weight loss or failure to gain weight in previous 3 months, (3) positive tuberculin skin test, or (4) chest radiograph suggestive of PTB Age, months: median (IQR) 31 (19 to 57) Sex, female: not reported HIV infection: 15% Sample size included for analysis: 115 Clinical setting: outpatient and inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 15%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	No consensus has been reached about stool processing techniques on stool before Xpert; this study used centrifugation

Methodological quality

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

Nicol 2013 *(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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Nicol 2018

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 14 years of age with cough lasting longer than 2 weeks and ≥ 1 of the following: (1) household tuberculosis contact in prior 3 months, (2) weight loss or failure to gain weight in previous 3 months, (3) positive tuberculin skin test, or (4) chest radiograph suggestive of PTB Age, months: median (IQR) 33 (15 to 74) Sex, female: 49% HIV infection: 19% Sample size included for analysis: 367 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: research laboratory Country: South Africa World Bank income classification: middle income High TB burden country: yes

Nicol 2018 *(Continued)*

	High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 20%
Index tests	Xpert Ultra and Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were performed within pre-specified time period
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?	Unclear		
Did the study avoid inappropriate exclusions?	No		
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	

Nicol 2018 *(Continued)*

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

Orikiriza 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 1 month to 14 years of age with presumptive TB defined as presence of ≥ 1 clinical sign suggestive of TB or TB contact history with abnormal chest X-ray, or any child with chest X-ray suggestive of TB Age, months: not reported Sex, female: 45% HIV infection: 30% Sample size included for analysis: 357 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: intermediate Country: Uganda World Bank income classification: low income High TB burden country: no High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 4%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis

Orikiriza 2018 *(Continued)*

	Solid and liquid cultures (LJ and MGIT); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were obtained within pre-specified time period
Comparative	
Notes	No consensus method for stool processing before Xpert is known; this study used centrifugation

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
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			

Orikiriza 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?	Yes		
Could the patient flow have introduced bias?		Low risk	

Pang 2014

Study characteristics			
Patient Sampling	Cross-sectional, consecutive, prospective		
Patient characteristics and setting	Presenting signs and symptoms: TB suspects had at least 1 of the following symptoms: cough for longer than 2 weeks, fever for longer than 2 weeks, weight loss, TB contact history, and radiological features Age, months: range 0 to 180 Sex, female: 39% HIV infection: not reported Sample size included for analysis: 211 Clinical setting: inpatient Laboratory level where index test was performed: central Country: China World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 8%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard		
Flow and timing	Index and reference tests were collected within pre-specified time period		
Comparative			
Notes	Study included only smear-negative participants		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	No		

Pang 2014 *(Continued)*

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)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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?	No		
Could the patient flow have introduced bias?		High risk	

Rachow 2012

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children with 6 weeks to 14 years of clinical signs of tuberculosis were enrolled in the study and were prospectively followed up for a minimum of 12 months. All children had ≥ 1 of the following symptoms: persistent un-

Rachow 2012 *(Continued)*

	remitting cough for.21 days; repeated episodes of fever within the last 21 days; weight loss or failure to thrive within the previous 3 months; or signs and symptoms suggestive of extrapulmonary tuberculosis Age, months: median (IQR) 70 (29 to 170) Sex, female: 48% HIV infection: 51% Sample size included for analysis: 129 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: research laboratory Country: Tanzania World Bank income classification: low income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 22%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (LJ and MGIT); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
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	

Rachow 2012 *(Continued)*

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

Reither 2015

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: ≥ 1 of the following inclusion criteria had to be met: persistent non-remitting cough longer than 14 days not responding to a course of antibiotics; repeated episodes of fever within the last 14 days not responding to a course of antibiotics, after malaria has been excluded; weight loss or failure to thrive within previous 3 months Age, months: median (IQR) 67 (67 to 118) Sex, female: 51% HIV infection: 44% Sample size included for analysis: 356 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: research laboratory Country: Uganda and Tanzania World Bank income classification: low income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 10%

Reither 2015 *(Continued)*

Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (MGIT and LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	

Reither 2015 *(Continued)*

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

Sabi 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children must have had 1 of the following symptoms: persistent non-remitting cough longer than 14 days not responding to antibiotics; repeated episodes of fever within the last 14 days not responding to antibiotics, after malaria has been excluded; weight loss or failure to thrive during previous 3 months; signs and symptoms suggestive of extrapulmonary TB Age, months: median (IQR) 65 (18 to 120) Sex, female: 43% HIV infection: 52% Sample size included for analysis: 215 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: research laboratory Country: Tanzania World Bank income classification: low income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 13%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (MGIT and LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	Ultra was performed on frozen specimens
Methodological quality	

Sabi 2018 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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 interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Sabi 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?	Yes		
Could the patient flow have introduced bias?		Low risk	

Saini 2018

Study characteristics			
Patient Sampling	Cross-sectional, manner of selection not reported, prospective		
Patient characteristics and setting	Presenting signs and symptoms: cough for longer than 2 weeks, fever, lethargy, contact with an adult patient with TB, positive tuberculin skin test, or chest radiograph consistent with TB. In addition, the patient needed to have negative testing by AFB smear and Xpert before moving to bronchoscopy for BAL Age, months: median (IQR) 120 (66 to 156) Sex, female: 53% HIV infection: 0% Sample size included for analysis: 41 Clinical setting: inpatient Laboratory level where index test was performed: central Country: India World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 27%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard		
Flow and timing	Participants were enrolled for BAL sample collection if they had probable TB and negative testing by AFB smear and Xpert by standard less invasive methods		
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?	Unclear		

Saini 2018 *(Continued)*

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

Sekadde 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: persistent cough of 2 weeks or longer and 1 of the following: household TB contact, unexplained

Sekadde 2013 *(Continued)*

	weight loss or failure to gain weight, unexplained fever for 2 weeks or longer Age, months: median (IQR) 36 (16 to 75) Sex, female: 46% HIV infection: 41% Sample size included for analysis: 235 Clinical setting: outpatient Laboratory level where index test was performed: central Country: Uganda World Bank income classification: low income High TB burden country: no High TB/HIV burden country: yes High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 14%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (MGIT and LJ)
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
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)			

Sekadde 2013 *(Continued)*

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

Singh M 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: ≥ 1 of the following: persistent fever and/or cough for ≥ 2 weeks, loss of weight/no weight gain, and history of contact with an infectious TB case Age, months: median (IQR) 64 (2 to 144) Sex, female: 38% HIV infection: not reported Sample size included for analysis: 50 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: India World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 24%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period

Singh M 2016 *(Continued)*

Comparative	
Notes	IS and GLA samples were combined; study was analysed as a sputum specimen

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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		

Singh M 2016 *(Continued)*

Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Solomons 2015

Study characteristics			
Patient Sampling	Cross-sectional, manner of selection not reported, prospective		
Patient characteristics and setting	Presenting signs and symptoms: age 3 months to 13 years with clinical suspicion of meningitis, CSF sample collected for fluorescent auramine-O microscopy, TB culture, Xpert assays Age, months: median (IQR) 36 (21 to 54) Sex, female: 44% HIV infection: 8% Sample size included for analysis: 101 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 12%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Tuberculous meningitis MGIT; composite reference standard; clinical reference standard		
Flow and timing	Index and reference tests were collected in pre-specified time period		
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?	Unclear		
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?			Low concern

Solomons 2015 *(Continued)*

DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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	

Togun 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: unremitting cough ≥ 14 days and ≥ 1 of fever, weight loss or failure to thrive, malaise or fatigue, haemoptysis, night sweats, or enlarged cervical lymph nodes Age, months: median (IQR) 72 (36 to 108) Sex, female: 47% HIV infection: 0% Sample size included for analysis: 487 Clinical setting: outpatient Laboratory level where index test was performed: central

Togun 2015 *(Continued)*

	Country: Gambia World Bank income classification: low income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 3%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (MGIT or LJ); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Togun 2015 *(Continued)*

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

Tortoli 2012

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, retrospective
Patient characteristics and setting	Presenting signs and symptoms: Not reported Age, months: median 84 Sex, female: not reported HIV infection: not reported Sample size included for analysis: 174 pulmonary tuberculosis; 89 LNTB; 43 TBM Clinical setting: laboratory Laboratory level where index test was performed: central Country: Italy World Bank income classification: high income High TB burden country: no High TB/HIV burden country: no High MDR-TB burden country: no Prevalence of tuberculosis cases in the study: 22% PTB; 17% LNTB; 9% TBM
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	PTB, LNTB, TBM Solid and liquid culture (LJ and MGIT)
Flow and timing	
Comparative	
Notes	
Methodological quality	

Tortoli 2012 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
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		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		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?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Vadwai 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: TBM symptoms included irritability, restlessness, neck stiffness, headache persistent for 2 to 3 weeks, vomiting, seizures, and changes in mental condition or behaviour. LNTB symptoms included enlargement of lymph nodes and mass formation in the neck Age, months: median (IQR) 66 (12 to 168) Sex, female: not reported HIV infection: 3% Sample size included for analysis: 14: 5 LNTB; 9 TBM Clinical setting: inpatient Laboratory level where index test was performed: central Country: India World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 20% LNTB and TBM
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Lymph node TB and tuberculous meningitis Solid and liquid culture (LJ and MGIT)
Flow and timing	Index and reference tests were collected within pre-specified time period
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		
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		

Vadwai 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	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	

Walters 2014

Study characteristics	
Patient Sampling	Cross-sectional, convenience, prospective
Patient characteristics and setting	Presenting signs and symptoms: chronic respiratory symptoms, contact with a known TB source case or a reactive Mantoux skin test in combination with any of the following: severe life-threatening intrathoracic large airway obstruction, radiographic evidence of complicated intrathoracic disease, or suspicion of drug-resistant TB based on the susceptibility pattern of an adult source case; none of the bacteriological samples taken from the child to date had been positive Age, months: median (IQR) 16 (5 to 132) Sex, female: 43% HIV infection: 14% Sample size included for analysis: 14 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes

Walters 2014 *(Continued)*

	High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 60%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	Study on BAL samples

Methodological quality

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

Walters 2014 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Walters 2017a

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: 1 or more of cough ≥ 2 weeks, unexplained fever of ≥ 1 week, or poor growth or weight loss over preceding 3 months. Also included were children with any duration of cough, if 1 or more of the following were present: exposure to an identified TB source case in the past 12 months, positive tuberculin skin test if previously negative or unknown, or chest radiograph suggestive of TB as assessed by the study clinician. Infants younger than 3 months were also eligible if they had pneumonia unresponsive to appropriate antimicrobials, or unexplained and unresponsive sepsis syndrome Age, months: median (IQR) 16 (9 to 29) Sex, female: 48% HIV infection: 13% Sample size included for analysis: 379 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 18%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	

Walters 2017a *(Continued)*

Notes	No consensus has been reached for stool processing before Xpert; this study used centrifugation

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Walters 2017a *(Continued)*

Could the patient flow have introduced bias?	Low risk

Walters 2018a

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: well-defined TB symptoms or shorter history of cough with known TB exposure, positive tuberculin skin test, or chest radiographic changes of concern for tuberculosis Age, months: median (IQR) 16 (11 to 29) Sex, female: 44% HIV infection: 13% Sample size included for analysis: 244 Clinical setting: inpatient and outpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 8%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	No consensus protocol for stool processing before Xpert is available; this study reported on stool filtration and swab processing

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

Walters 2018a *(Continued)*

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

Yin 2014

Study characteristics	
Patient Sampling	Cross-sectional, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: children aged 18 years or younger were eligible for enrolment if they had been admitted to hospital, with suspected PTB, having a cough for longer than 2 weeks, and a chest radiograph suggesting the need for routine fibreoptic bronchoscopy Age, months: mean 73 Sex, female: 56% HIV infection: not reported Sample size included for analysis: 255

Yin 2014 *(Continued)*

	Clinical setting: inpatient Laboratory level where index test was performed: central Country: China World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 10%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis Solid and liquid culture (LJ and MGIT); composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	
Notes	Xpert was performed on BAL samples

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
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)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		

Yin 2014 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?		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

Zar 2012

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 14 years with cough lasting longer than 2 weeks and at least 1 of the following: household tuberculosis contact in previous 3 months, weight loss or failure to gain weight in previous 3 months, positive tuberculin skin test, or chest radiograph suggestive of PTB Age, months: median (IQR) 19 (11 to 38) Sex, female: 45% HIV infection: 22% Sample size included for analysis: 474 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 17%
Index tests	Xpert MTB/RIF
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard
Flow and timing	Index and reference tests were collected within pre-specified time period
Comparative	

Zar 2012 *(Continued)*

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

Zar 2013

Study characteristics			
Patient Sampling	Cohort, consecutive, prospective		
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 14 years of age with cough lasting longer than 2 weeks and at least 1 of the following: household tuberculosis contact in previous 3 months, weight loss or failure to gain weight in previous 3 months, positive tuberculin skin test, or chest radiograph suggestive of PTB Age, months: median (IQR) 38 (21 to 57) Sex, female: 53% HIV infection: 8% Sample size included for analysis: 384 Clinical setting: outpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 8%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard		
Flow and timing	Index and reference tests were collected within pre-specified time period		
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		
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		

Zar 2013 *(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)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Zar 2019

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: children 0 to 14 years of age with cough lasting longer than 2 weeks and at least 1 of the following: household tuberculosis contact in previous 3 months, weight loss or failure to gain weight in previous 3 months, positive tuberculin skin test, or chest radiograph suggestive of PTB Age, months: median (IQR) 23 (14 to 47) Sex, female: not reported HIV infection: 16% Sample size included for analysis: 195 Clinical setting: inpatient Laboratory level where index test was performed: intermediate Country: South Africa World Bank income classification: middle income High TB burden country: yes High TB/HIV burden country: yes

Zar 2019 *(Continued)*

	High MDR-TB burden country: yes Prevalence of tuberculosis cases in the study: 21%		
Index tests	Xpert MTB/RIF		
Target condition and reference standard(s)	Pulmonary tuberculosis MGIT; composite reference standard; clinical reference standard		
Flow and timing	Index and reference tests were collected within pre-specified time period		
Comparative			
Notes	Xpert Ultra test was performed on frozen specimens		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	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

Zar 2019 *(Continued)*

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

AFB: acid-fast bacillus.
BAL: bronchoalveolar lavage.
GLA: gastric lavage aspirate.
IQR: interquartile ratio.
IS: induced sputum.
LJ: Löwenstein-Jensen.
LNTB: lymph node tuberculosis.
M tuberculosis: *Mycobacterium tuberculosis*.
MDR-TB: multi-drug-resistant tuberculosis.
MGIT: mycobacteria growth indicator tube.
MTB/RIF: *Mycobacterium tuberculosis* complex and resistance to rifampin.

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

Study	Reason for exclusion
Ali 2017	Unable to separate paediatric data from adult data
Atashi 2017	Adult population
Atehortúa Muñoz 2017	Not a diagnostic accuracy study
Azevedo 2018	Adult population
Ballif 2015	Not a diagnostic accuracy study
Banada 2016	Case-control study
Biadglegne 2014	Unable to separate paediatric data from adult data

Study	Reason for exclusion
Bojang 2016	Unable to separate paediatric data from adult data
Che 2017	Adult population
Cox 2014	Adult population
Cross 2014	Unable to separate paediatric data from adult data
Diallo 2016	Unable to separate paediatric data from adult data
DiNardo 2016	Not a diagnostic accuracy study
DiNardo 2018	Index test not studied
Ejeh 2018	Unable to separate paediatric data from adult data
Gautam 2018	Unable to separate paediatric data from adult data
Gelalcha 2017	Unable to separate paediatric data from adult data
Geleta 2015	Adult population
Ghariani 2015	Unable to separate paediatric data from adult data
Giang 2015	Unable to extract data by sample type
Guajardo-Lara 2018	Insufficient data
Gulla 2019	Not a diagnostic accuracy study
Hakim 2017	Not a diagnostic accuracy study
Helb 2010	Adult population
Horo 2017	Unable to separate paediatric data from adult data
Huh 2014	Adult population
Kuyinu 2018	Inappropriate reference standard
Lopez 2019	Index text not studied
Lu J 2017	Screening for clinical tuberculosis before enrolment
Lu Y 2018	Adult population
Malik 2018	Not a diagnostic accuracy study
Marcy 2018	Duplicate data for Marcy 2016
Masenga 2017	Unable to separate paediatric data from adult data
Mekonnen 2015	Adult population
Memon 2018	Clinical diagnosis of tuberculosis established at enrolment

Study	Reason for exclusion
Metaferia 2018	Inappropriate reference standard
Mijovic 2018	Not a diagnostic accuracy study
Modi 2016	Index test not studied
Mulenga 2015	Index test not studied
Naidoo 2016	Not a diagnostic accuracy study
Nair 2016	Not a diagnostic accuracy study
Nansumba 2016	Index test not studied
Nataprawira 2016	Not a diagnostic accuracy study
Ncube 2017	Not a diagnostic accuracy study
Nduba 2015	Index text not studied
Ngabonziza 2016	Adult population
Ntinginya 2012	Not a diagnostic accuracy study
Opota 2019	Adult population
Pandey 2017	Unable to separate paediatric data from adult data
Pink 2016	Unable to separate paediatric data from adult data
Planting 2014	Not a diagnostic accuracy study
Raizada 2014	Inappropriate reference standard
Raizada 2015a	Inappropriate reference standard
Raizada 2015b	Inappropriate reference standard
Raizada 2018b	Inappropriate reference standard
Raizada 2018c	Inappropriate reference standard
Rathour 2019	Screening for clinical tuberculosis before enrolment
Rebecca 2018	Case-control study
Rivera 2017	Not a diagnostic accuracy study
Sabi 2016	Not a diagnotic accuracy study
Sachdeva 2015	Not a diagnostic accuracy study
Sanchini 2014	Not a diagnostic accuracy study
Sander 2019	Adult population

Study	Reason for exclusion
Sanjuan-Jimenez 2015	Adult population
Schumacher 2016	Not a diagnostic accuracy study
Scott 2014	Unable to separate paediatric data from adult data
Shah 2016a	Insufficient data
Shah 2018	Not a diagnostic accuracy study
Shah 2019	Case-control study
Sharma 2015	Unable to separate paediatric data from adult data
Sieiro 2018	Unable to separate paediatric data from adult data
Singh 2015	Clinical diagnosis of tuberculosis established at enrolment
Singh UB 2016	Adult population
Solomons 2016	Not a diagnostic accuracy study
Sureshbabu 2016	Unable to separate paediatric data from adult data
Tadesse 2015	Unable to separate paediatric data from adult data
Tafur 2018	Not a diagnostic accuracy study
Tang 2017	Adult population
Theron 2011	Adult population
Triasih 2015	Not a diagnostic accuracy study
Ullah 2017	Unable to separate paediatric data from adult data
Walters 2012	Insufficient data
Walters 2017b	Index text not studied
Walters 2018b	Not a diagnostic accuracy study
Zhang 2016	Insufficient data

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

ChiCTR1800015075

Study name	Diagnostic accuracy of Xpert MTB/RIF Ultra assay on diagnosing paediatric pulmonary tuberculosis
Target condition and reference standard(s)	Pulmonary tuberculosis

ChiCTR1800015075 *(Continued)*

Index and comparator tests	Xpert Ultra
Starting date	1 January 2018
Contact information	Xuhui Liu; liuxuhui@shaphc.org
Notes	

NCT03831906

Study name	TB-speed pneumonia
Target condition and reference standard(s)	Tuberculosis, pneumonia
Index and comparator tests	Xpert Ultra
Starting date	20 March 2019
Contact information	Aurelia Vessiere, PhD; aurelia.vessiere@u-bordeaux.fr
Notes	

MTB/RIF: *Mycobacterium tuberculosis* complex and resistance to rifampin.
TB: tuberculosis.

DATA

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

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Xpert MTB/RIF, sputum, culture	25	6812
2 Xpert MTB/RIF, sputum, composite reference standard	17	4382
3 Xpert Ultra, sputum, culture	3	697
4 Xpert Ultra, sputum, composite reference standard	3	753
5 Xpert MTB/RIF, gastric aspirate specimen, culture	15	3487
6 Xpert MTB/RIF, gastric aspirate specimen, composite reference standard	7	948
7 Xpert MTB/RIF, stool, culture	11	1592
8 Xpert MTB/RIF, stool, composite reference standard	10	1739
9 Xpert MTB/RIF, nasopharyngeal aspirate, culture	4	1125

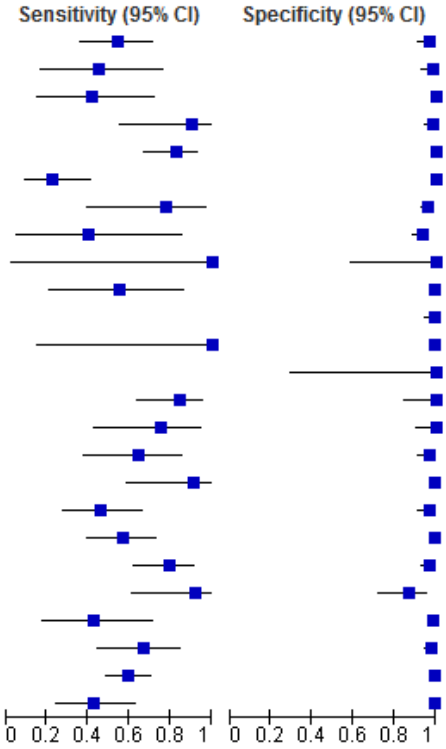
Test	No. of studies	No. of participants
10 Xpert Ultra, nasopharyngeal aspirate, culture	1	195
11 Xpert MTB/RIF, sputum, culture, direct comparison	3	609
12 Xpert Ultra, sputum, culture, direct comparison	3	697
13 Xpert MTB/RIF, sputum, smear-positive, culture	11	103
14 Xpert MTB/RIF, sputum, smear-negative, culture	13	3121
15 Xpert MTB/RIF, sputum, HIV-positive, culture	11	694
16 Xpert MTB/RIF, sputum, HIV-negative, culture	12	2784
17 Xpert Ultra, sputum, HIV-positive, culture	1	32
18 Xpert Ultra, sputum, HIV-negative, culture	1	157
19 Xpert MTB/RIF, gastric aspirate specimen, HIV-positive, culture	3	634
20 Xpert MTB/RIF, gastric aspirate specimen, HIV-negative, culture	4	1531
21 Xpert MTB/RIF, stool, HIV-positive, culture	4	526
22 Xpert MTB/RIF, stool, HIV-negative, culture	4	369
23 Xpert MTB/RIF, sputum, 5 to 14 years, culture	8	806
24 Xpert MTB/RIF, sputum, 0 to 4 years, culture	10	2184
25 Xpert MTB/RIF, induced sputum, 5 to 14, culture	5	627
26 Xpert MTB/RIF, induced sputum, 0 to 4 years, culture	7	2062
27 Xpert MTB/RIF, gastric aspirate specimen, 0 to 4 years, culture	4	1795
28 Xpert MTB/RIF, sputum, culture, high tuberculosis burden, yes	19	5268
29 Xpert MTB/RIF, sputum, culture, high tuberculosis burden, no	6	1469
30 Xpert MTB/RIF, sputum, inpatients, culture	4	869
31 Xpert MTB/RIF, sputum, outpatients, culture	4	1140
32 Xpert MTB/RIF, CSF, culture	8	268
33 Xpert MTB/RIF, CSF, composite reference standard	2	155
34 Xpert MTB/RIF, lymph node specimen, culture	7	211
35 Xpert MTB/RIF, lymph node specimen, composite reference standard	3	107
36 Xpert MTB/RIF, rifampicin resistance, any specimen	14	326
37 Xpert MTB/RIF, sputum, multiple tests, culture	5	1925

Test	No. of studies	No. of participants
38 Xpert MTB/RIF, sputum, initial test, culture	5	1939
39 Xpert MTB/RIF, gastric aspirate specimen, multiple tests, culture	1	921
40 Xpert MTB/RIF, gastric aspirate specimen, initial test, culture	1	935
41 Xpert MTB/RIF, stool, multiple tests, culture	1	247
42 Xpert MTB/RIF, stool, initial test, culture	1	236
43 Xpert MTB/RIF, nasopharyngeal aspirate, multiple tests, culture	2	705
44 Xpert MTB/RIF, nasopharyngeal aspirate, initial test, culture	2	705
45 Xpert Ultra, sputum, multiple tests, culture	1	135
46 Xpert Ultra, sputum, initial test, culture	1	135
47 Xpert Ultra, nasopharyngeal aspirate, multiple tests, culture	1	130
48 Xpert Ultra, nasopharyngeal aspirate, initial test, culture	1	130
49 Xpert MTB/RIF, sputum, multiple cultures	12	3280
50 Xpert MTB/RIF, sputum, single culture	13	3442
51 Xpert MTB/RIF, induced sputum, culture	15	3844
52 Xpert MTB/RIF, gastric aspirate specimen, 5 to 14, culture	2	154
53 Xpert MTB/RIF, nasopharyngeal aspirate, 5 to 14, culture	1	70
54 Xpert MTB/RIF, nasopharyngeal aspirate, 0 to 4, culture	1	404

Test 1. Xpert MTB/RIF, sputum, culture

Xpert MTB/RIF, sputum, culture

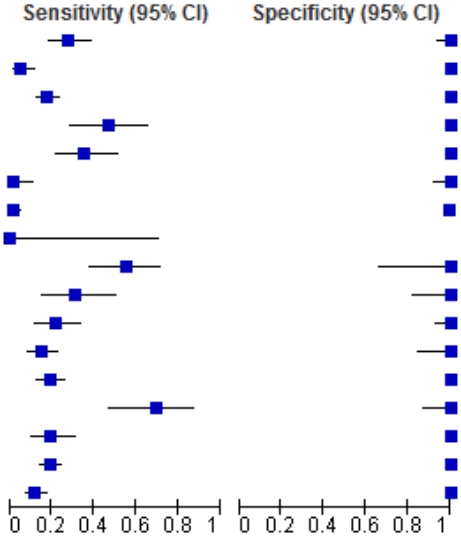
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	19	3	16	96	0.54 [0.37, 0.71]	0.97 [0.91, 0.99]
Atwebembeire 2016	5	1	6	73	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]
Bacha 2017	5	0	7	252	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]
Bates 2013	9	2	1	130	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Brent 2017	33	0	7	1064	0.82 [0.67, 0.93]	1.00 [1.00, 1.00]
Bunyasi 2015	7	0	24	908	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
Das 2019	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
Gous 2015	5	3	4	333	0.56 [0.21, 0.86]	0.99 [0.97, 1.00]
Hanrahan 2018	0	1	0	105	Not estimable	0.99 [0.95, 1.00]
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Malbruny 2011	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Nicol 2013	11	3	6	95	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]
Orikiriza 2018	10	3	1	325	0.91 [0.59, 1.00]	0.99 [0.97, 1.00]
Rachow 2012	13	3	15	98	0.46 [0.28, 0.66]	0.97 [0.92, 0.99]
Reither 2015	21	2	16	411	0.57 [0.39, 0.73]	1.00 [0.98, 1.00]
Sekadde 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
Singh M 2016	11	5	1	33	0.92 [0.62, 1.00]	0.87 [0.72, 0.96]
Togun 2015	6	6	8	467	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Walters 2017a	16	6	8	240	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]
Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 2. Xpert MTB/RIF, sputum, composite reference standard

Xpert MTB/RIF, sputum, composite reference standard

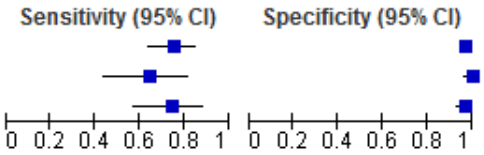
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	22	0	57	55	0.28 [0.18, 0.39]	1.00 [0.94, 1.00]
Bacha 2017	5	0	85	168	0.06 [0.02, 0.12]	1.00 [0.98, 1.00]
Brent 2017	33	0	152	892	0.18 [0.13, 0.24]	1.00 [1.00, 1.00]
Chipinduro 2017	15	0	17	186	0.47 [0.29, 0.65]	1.00 [0.98, 1.00]
Chisti 2014	16	0	29	166	0.36 [0.22, 0.51]	1.00 [0.98, 1.00]
Hanrahan 2018	1	0	47	45	0.02 [0.00, 0.11]	1.00 [0.92, 1.00]
LaCourse 2014	2	1	128	167	0.02 [0.00, 0.05]	0.99 [0.97, 1.00]
Malbruny 2011	0	0	3	0	0.00 [0.00, 0.71]	Not estimable
Nhu 2013	21	0	17	9	0.55 [0.38, 0.71]	1.00 [0.66, 1.00]
Nicol 2011	9	0	20	19	0.31 [0.15, 0.51]	1.00 [0.82, 1.00]
Nicol 2013	14	0	51	50	0.22 [0.12, 0.33]	1.00 [0.93, 1.00]
Rachow 2012	16	0	91	22	0.15 [0.09, 0.23]	1.00 [0.85, 1.00]
Reither 2015	28	0	119	209	0.19 [0.13, 0.26]	1.00 [0.98, 1.00]
Singh M 2016	16	0	7	27	0.70 [0.47, 0.87]	1.00 [0.87, 1.00]
Togun 2015	12	0	50	425	0.19 [0.10, 0.31]	1.00 [0.99, 1.00]
Zar 2012	54	0	227	193	0.19 [0.15, 0.24]	1.00 [0.98, 1.00]
Zar 2013	22	0	158	204	0.12 [0.08, 0.18]	1.00 [0.98, 1.00]



Test 3. Xpert Ultra, sputum, culture

Xpert Ultra, sputum, culture

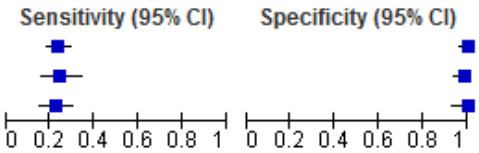
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	55	9	18	285	0.75 [0.64, 0.85]	0.97 [0.94, 0.99]
Sabi 2018	18	0	10	107	0.64 [0.44, 0.81]	1.00 [0.97, 1.00]
Zar 2019	26	5	9	155	0.74 [0.57, 0.88]	0.97 [0.93, 0.99]



Test 4. Xpert Ultra, sputum, composite reference standard

Xpert Ultra, sputum, composite reference standard

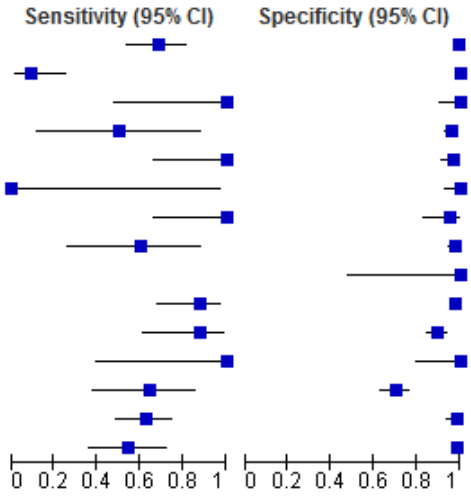
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	64	0	206	97	0.24 [0.19, 0.29]	1.00 [0.96, 1.00]
Sabi 2018	22	2	67	105	0.25 [0.16, 0.35]	0.98 [0.93, 1.00]
Zar 2019	31	0	108	51	0.22 [0.16, 0.30]	1.00 [0.93, 1.00]



Test 5. Xpert MTB/RIF, gastric aspirate specimen, culture

Xpert MTB/RIF, gastric aspirate specimen, culture

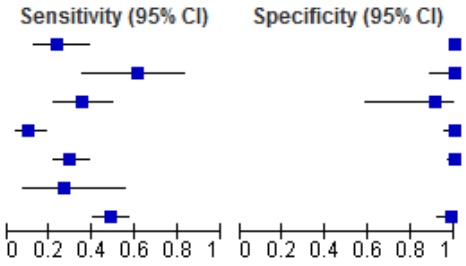
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	33	5	15	735	0.69 [0.54, 0.81]	0.99 [0.98, 1.00]
Bunyasi 2015	3	1	29	902	0.09 [0.02, 0.25]	1.00 [0.99, 1.00]
Causse 2011	5	0	0	38	1.00 [0.48, 1.00]	1.00 [0.91, 1.00]
Chisti 2014	3	8	3	200	0.50 [0.12, 0.88]	0.96 [0.93, 0.98]
Das 2019	9	3	0	94	1.00 [0.66, 1.00]	0.97 [0.91, 0.99]
Hanrahan 2018	0	0	1	49	0.00 [0.00, 0.97]	1.00 [0.93, 1.00]
Hasan 2017	9	2	0	38	1.00 [0.66, 1.00]	0.95 [0.83, 0.99]
LaCourse 2018	6	3	4	151	0.60 [0.26, 0.88]	0.98 [0.94, 1.00]
Malbruny 2011	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Marcy 2016	21	4	3	207	0.88 [0.68, 0.97]	0.98 [0.95, 0.99]
Myo 2018	14	22	2	193	0.88 [0.62, 0.98]	0.90 [0.85, 0.93]
Nhu 2013	4	0	0	16	1.00 [0.40, 1.00]	1.00 [0.79, 1.00]
Pang 2014	11	58	6	136	0.65 [0.38, 0.86]	0.70 [0.63, 0.76]
Tortoli 2012	37	2	22	113	0.63 [0.49, 0.75]	0.98 [0.94, 1.00]
Walters 2017a	18	3	15	226	0.55 [0.36, 0.72]	0.99 [0.96, 1.00]



Test 6. Xpert MTB/RIF, gastric aspirate specimen, composite reference standard

Xpert MTB/RIF, gastric aspirate specimen, composite reference standard

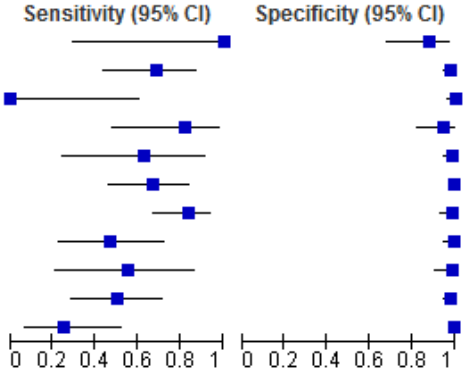
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chisti 2014	11	0	35	168	0.24 [0.13, 0.39]	1.00 [0.98, 1.00]
Hasan 2017	11	0	7	32	0.61 [0.36, 0.83]	1.00 [0.89, 1.00]
Kasa Tom 2018	18	1	33	10	0.35 [0.22, 0.50]	0.91 [0.59, 1.00]
LaCourse 2018	9	0	76	80	0.11 [0.05, 0.19]	1.00 [0.95, 1.00]
Myo 2018	36	0	85	110	0.30 [0.22, 0.39]	1.00 [0.97, 1.00]
Nhu 2013	4	0	11	0	0.27 [0.08, 0.55]	Not estimable
Pang 2014	68	1	72	70	0.49 [0.40, 0.57]	0.99 [0.92, 1.00]



Test 7. Xpert MTB/RIF, stool, culture

Xpert MTB/RIF, stool, culture

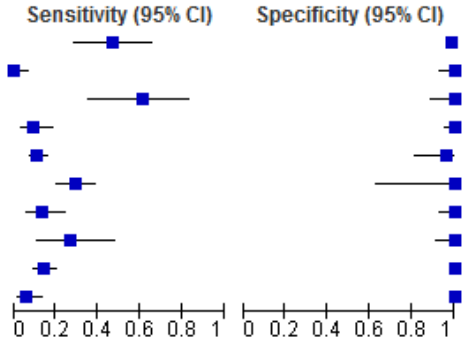
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andriyoko 2019	3	3	0	21	1.00 [0.29, 1.00]	0.88 [0.68, 0.97]
Chipinduro 2017	13	4	6	195	0.68 [0.43, 0.87]	0.98 [0.95, 0.99]
Hanrahan 2018	0	0	4	96	0.00 [0.00, 0.60]	1.00 [0.96, 1.00]
Hasan 2017	9	2	2	36	0.82 [0.48, 0.98]	0.95 [0.82, 0.99]
LaCourse 2018	5	2	3	137	0.63 [0.24, 0.91]	0.99 [0.95, 1.00]
Marcy 2016	18	1	9	223	0.67 [0.46, 0.83]	1.00 [0.98, 1.00]
Moussa 2016	30	1	6	78	0.83 [0.67, 0.94]	0.99 [0.93, 1.00]
Nicol 2013	8	1	9	97	0.47 [0.23, 0.72]	0.99 [0.94, 1.00]
Orikiriza 2018	5	1	4	54	0.56 [0.21, 0.86]	0.98 [0.90, 1.00]
Walters 2017a	12	6	12	240	0.50 [0.29, 0.71]	0.98 [0.95, 0.99]
Walters 2018a	4	1	12	219	0.25 [0.07, 0.52]	1.00 [0.97, 1.00]



Test 8. Xpert MTB/RIF, stool, composite reference standard

Xpert MTB/RIF, stool, composite reference standard

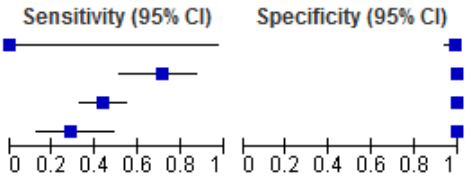
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	15	2	17	184	0.47 [0.29, 0.65]	0.99 [0.96, 1.00]
Hanrahan 2018	0	0	48	48	0.00 [0.00, 0.07]	1.00 [0.93, 1.00]
Hasan 2017	11	0	7	32	0.61 [0.36, 0.83]	1.00 [0.89, 1.00]
LaCourse 2018	7	0	67	74	0.09 [0.04, 0.19]	1.00 [0.95, 1.00]
Marcy 2016	28	1	217	26	0.11 [0.08, 0.16]	0.96 [0.81, 1.00]
Moussa 2016	31	0	76	8	0.29 [0.21, 0.39]	1.00 [0.63, 1.00]
Nicol 2013	9	0	56	50	0.14 [0.07, 0.25]	1.00 [0.93, 1.00]
Orikiriza 2018	7	0	19	41	0.27 [0.12, 0.48]	1.00 [0.91, 1.00]
Walters 2017a	24	0	146	209	0.14 [0.09, 0.20]	1.00 [0.98, 1.00]
Walters 2018a	6	0	88	185	0.06 [0.02, 0.13]	1.00 [0.98, 1.00]



Test 9. Xpert MTB/RIF, nasopharyngeal aspirate, culture

Xpert MTB/RIF, nasopharyngeal aspirate, culture

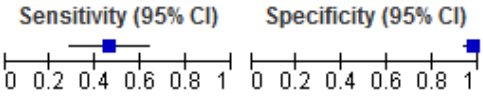
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hanrahan 2018	0	1	1	81	0.00 [0.00, 0.97]	0.99 [0.93, 1.00]
Marcy 2016	20	1	8	230	0.71 [0.51, 0.87]	1.00 [0.98, 1.00]
Zar 2012	38	1	49	386	0.44 [0.33, 0.55]	1.00 [0.99, 1.00]
Zar 2013	8	1	20	280	0.29 [0.13, 0.49]	1.00 [0.98, 1.00]



Test 10. Xpert Ultra, nasopharyngeal aspirate, culture

Xpert Ultra, nasopharyngeal aspirate, culture

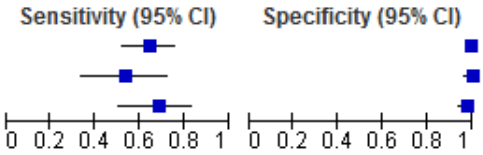
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2019	16	4	19	156	0.46 [0.29, 0.63]	0.97 [0.94, 0.99]



Test 11. Xpert MTB/RIF, sputum, culture, direct comparison

Xpert MTB/RIF, sputum, culture, direct comparison

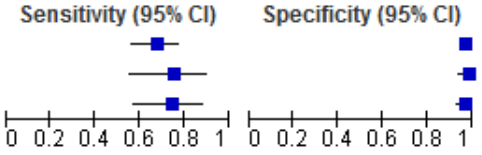
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	47	1	26	232	0.64 [0.52, 0.75]	1.00 [0.98, 1.00]
Sabi 2018	15	0	13	105	0.54 [0.34, 0.72]	1.00 [0.97, 1.00]
Zar 2019	24	3	11	132	0.69 [0.51, 0.83]	0.98 [0.94, 1.00]



Test 12. Xpert Ultra, sputum, culture, direct comparison

Xpert Ultra, sputum, culture, direct comparison

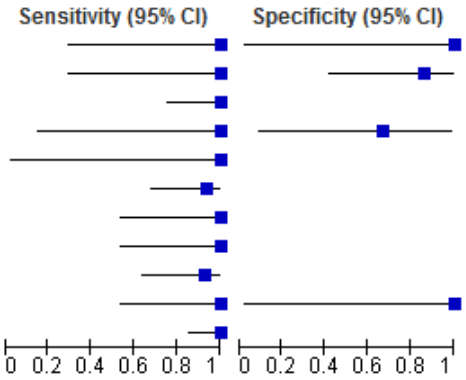
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nicol 2018	56	8	27	276	0.67 [0.56, 0.77]	0.97 [0.95, 0.99]
Sabi 2018	21	2	7	105	0.75 [0.55, 0.89]	0.98 [0.93, 1.00]
Zar 2019	26	5	9	155	0.74 [0.57, 0.88]	0.97 [0.93, 0.99]



Test 13. Xpert MTB/RIF, sputum, smear-positive, culture

Xpert MTB/RIF, sputum, smear-positive, culture

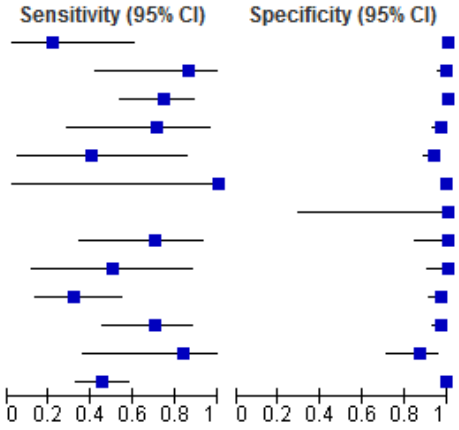
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacha 2017	3	0	0	1	1.00 [0.29, 1.00]	1.00 [0.03, 1.00]
Bates 2013	3	1	0	6	1.00 [0.29, 1.00]	0.86 [0.42, 1.00]
Brent 2017	13	0	0	0	1.00 [0.75, 1.00]	Not estimable
Chipinduro 2017	2	1	0	2	1.00 [0.16, 1.00]	0.67 [0.09, 0.99]
LaCourse 2014	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Nhu 2013	14	0	1	0	0.93 [0.68, 1.00]	Not estimable
Nicol 2011	6	0	0	0	1.00 [0.54, 1.00]	Not estimable
Rachow 2012	6	0	0	0	1.00 [0.54, 1.00]	Not estimable
Sekadde 2013	12	0	1	0	0.92 [0.64, 1.00]	Not estimable
Singh M 2016	6	0	0	1	1.00 [0.54, 1.00]	1.00 [0.03, 1.00]
Zar 2012	23	0	0	0	1.00 [0.85, 1.00]	Not estimable



Test 14. Xpert MTB/RIF, sputum, smear-negative, culture

Xpert MTB/RIF, sputum, smear-negative, culture

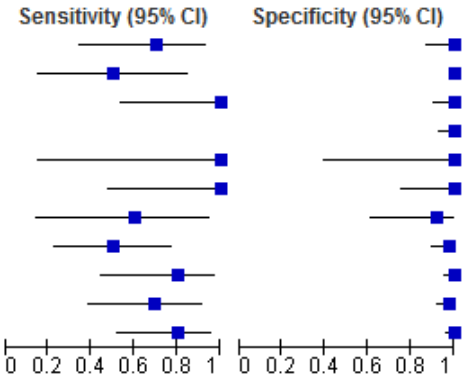
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacha 2017	2	0	7	251	0.22 [0.03, 0.60]	1.00 [0.99, 1.00]
Bates 2013	6	1	1	124	0.86 [0.42, 1.00]	0.99 [0.96, 1.00]
Brent 2017	20	0	7	1064	0.74 [0.54, 0.89]	1.00 [1.00, 1.00]
Chipinduro 2017	5	7	2	199	0.71 [0.29, 0.96]	0.97 [0.93, 0.99]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
LaCourse 2014	1	1	0	297	1.00 [0.03, 1.00]	1.00 [0.98, 1.00]
Malbruny 2011	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Nhu 2013	7	0	3	22	0.70 [0.35, 0.93]	1.00 [0.85, 1.00]
Nicol 2011	3	0	3	36	0.50 [0.12, 0.88]	1.00 [0.90, 1.00]
Rachow 2012	7	3	15	98	0.32 [0.14, 0.55]	0.97 [0.92, 0.99]
Sekadde 2013	14	7	6	194	0.70 [0.46, 0.88]	0.97 [0.93, 0.99]
Singh M 2016	5	5	1	32	0.83 [0.36, 1.00]	0.86 [0.71, 0.95]
Zar 2012	29	2	35	385	0.45 [0.33, 0.58]	0.99 [0.98, 1.00]



Test 15. Xpert MTB/RIF, sputum, HIV-positive, culture

Xpert MTB/RIF, sputum, HIV-positive, culture

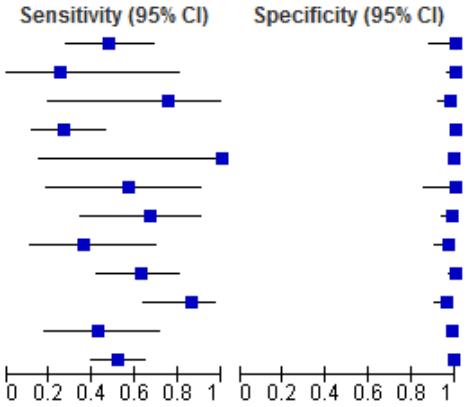
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	7	0	3	26	0.70 [0.35, 0.93]	1.00 [0.87, 1.00]
Bacha 2017	4	0	4	150	0.50 [0.16, 0.84]	1.00 [0.98, 1.00]
Bates 2013	6	0	0	38	1.00 [0.54, 1.00]	1.00 [0.91, 1.00]
LaCourse 2014	0	0	0	52	Not estimable	1.00 [0.93, 1.00]
Nhu 2013	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]
Nicol 2011	5	0	0	13	1.00 [0.48, 1.00]	1.00 [0.75, 1.00]
Nicol 2013	3	1	2	11	0.60 [0.15, 0.95]	0.92 [0.62, 1.00]
Rachow 2012	7	1	7	52	0.50 [0.23, 0.77]	0.98 [0.90, 1.00]
Reither 2015	8	0	2	80	0.80 [0.44, 0.97]	1.00 [0.95, 1.00]
Sekadde 2013	9	2	4	84	0.69 [0.39, 0.91]	0.98 [0.92, 1.00]
Zar 2012	12	0	3	92	0.80 [0.52, 0.96]	1.00 [0.96, 1.00]



Test 16. Xpert MTB/RIF, sputum, HIV-negative, culture

Xpert MTB/RIF, sputum, HIV-negative, culture

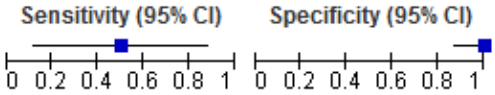
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	12	0	13	29	0.48 [0.28, 0.69]	1.00 [0.88, 1.00]
Bacha 2017	1	0	3	102	0.25 [0.01, 0.81]	1.00 [0.96, 1.00]
Bates 2013	3	2	1	84	0.75 [0.19, 0.99]	0.98 [0.92, 1.00]
Bunyasi 2015	8	0	22	893	0.27 [0.12, 0.46]	1.00 [1.00, 1.00]
LaCourse 2014	2	1	0	240	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nicol 2011	4	0	3	23	0.57 [0.18, 0.90]	1.00 [0.85, 1.00]
Nicol 2013	8	1	4	85	0.67 [0.35, 0.90]	0.99 [0.94, 1.00]
Rachow 2012	4	2	7	68	0.36 [0.11, 0.69]	0.97 [0.90, 1.00]
Reither 2015	17	0	10	127	0.63 [0.42, 0.81]	1.00 [0.97, 1.00]
Sekadde 2013	18	5	3	110	0.86 [0.64, 0.97]	0.96 [0.90, 0.99]
Togun 2015	6	6	8	487	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Zar 2012	35	2	32	293	0.52 [0.40, 0.65]	0.99 [0.98, 1.00]



Test 17. Xpert Ultra, sputum, HIV-positive, culture

Xpert Ultra, sputum, HIV-positive, culture

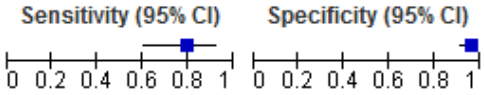
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2019	3	0	3	26	0.50 [0.12, 0.88]	1.00 [0.87, 1.00]



Test 18. Xpert Ultra, sputum, HIV-negative, culture

Xpert Ultra, sputum, HIV-negative, culture

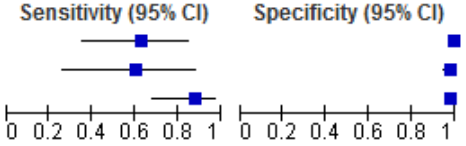
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2019	23	5	6	123	0.79 [0.60, 0.92]	0.96 [0.91, 0.99]



Test 19. Xpert MTB/RIF, gastric aspirate specimen, HIV-positive, culture

Xpert MTB/RIF, gastric aspirate specimen, HIV-positive, culture

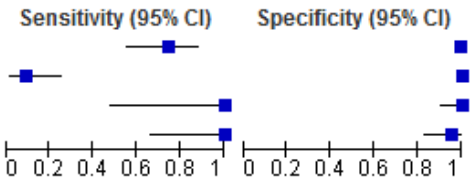
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	10	2	6	217	0.63 [0.35, 0.85]	0.99 [0.97, 1.00]
LaCourse 2018	6	3	4	151	0.60 [0.26, 0.88]	0.98 [0.94, 1.00]
Marcy 2016	21	4	3	207	0.88 [0.68, 0.97]	0.98 [0.95, 0.99]



Test 20. Xpert MTB/RIF, gastric aspirate specimen, HIV-negative, culture

Xpert MTB/RIF, gastric aspirate specimen, HIV-negative, culture

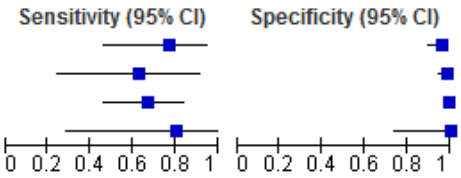
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	23	3	8	470	0.74 [0.55, 0.88]	0.99 [0.98, 1.00]
Bunyasi 2015	3	1	29	902	0.09 [0.02, 0.25]	1.00 [0.99, 1.00]
Causse 2011	5	0	0	38	1.00 [0.48, 1.00]	1.00 [0.91, 1.00]
Hasan 2017	9	2	0	38	1.00 [0.66, 1.00]	0.95 [0.83, 0.99]



Test 21. Xpert MTB/RIF, stool, HIV-positive, culture

Xpert MTB/RIF, stool, HIV-positive, culture

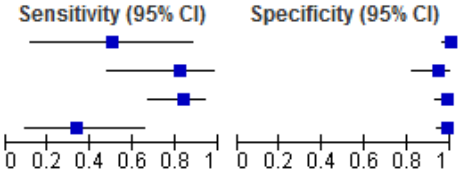
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	10	4	3	94	0.77 [0.46, 0.95]	0.96 [0.90, 0.99]
LaCourse 2018	5	2	3	137	0.63 [0.24, 0.91]	0.99 [0.95, 1.00]
Marcy 2016	18	1	9	223	0.67 [0.46, 0.83]	1.00 [0.98, 1.00]
Nicol 2013	4	0	1	12	0.80 [0.28, 0.99]	1.00 [0.74, 1.00]



Test 22. Xpert MTB/RIF, stool, HIV-negative, culture

Xpert MTB/RIF, stool, HIV-negative, culture

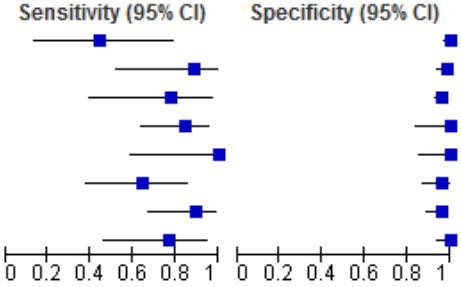
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	3	0	3	101	0.50 [0.12, 0.88]	1.00 [0.96, 1.00]
Hasan 2017	9	2	2	36	0.82 [0.48, 0.98]	0.95 [0.82, 0.99]
Moussa 2016	30	1	6	78	0.83 [0.67, 0.94]	0.99 [0.93, 1.00]
Nicol 2013	4	1	8	85	0.33 [0.10, 0.65]	0.99 [0.94, 1.00]



Test 23. Xpert MTB/RIF, sputum, 5 to 14 years, culture

Xpert MTB/RIF, sputum, 5 to 14 years, culture

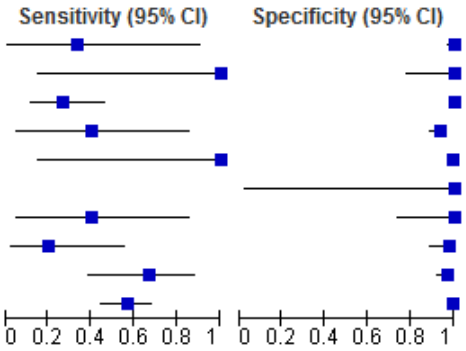
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacha 2017	4	0	5	143	0.44 [0.14, 0.79]	1.00 [0.97, 1.00]
Bates 2013	8	2	1	114	0.89 [0.52, 1.00]	0.98 [0.94, 1.00]
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Nhu 2013	21	0	4	21	0.84 [0.64, 0.95]	1.00 [0.84, 1.00]
Nicol 2011	7	0	0	24	1.00 [0.59, 1.00]	1.00 [0.86, 1.00]
Rachow 2012	11	2	6	52	0.65 [0.38, 0.86]	0.96 [0.87, 1.00]
Sekadde 2013	17	3	2	71	0.89 [0.67, 0.99]	0.96 [0.89, 0.99]
Zar 2012	10	0	3	57	0.77 [0.46, 0.95]	1.00 [0.94, 1.00]



Test 24. Xpert MTB/RIF, sputum, 0 to 4 years, culture

Xpert MTB/RIF, sputum, 0 to 4 years, culture

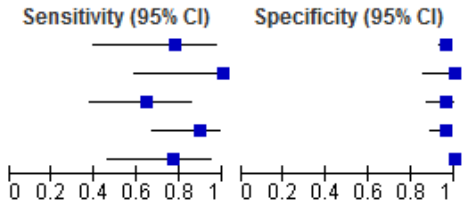
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacha 2017	1	0	2	109	0.33 [0.01, 0.91]	1.00 [0.97, 1.00]
Bates 2013	2	0	0	15	1.00 [0.16, 1.00]	1.00 [0.78, 1.00]
Bunyasi 2015	8	0	22	893	0.27 [0.12, 0.46]	1.00 [1.00, 1.00]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nhu 2013	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Nicol 2011	2	0	3	12	0.40 [0.05, 0.85]	1.00 [0.74, 1.00]
Rachow 2012	2	1	8	46	0.20 [0.03, 0.56]	0.98 [0.89, 1.00]
Sekadde 2013	10	4	5	123	0.67 [0.38, 0.88]	0.97 [0.92, 0.99]
Zar 2012	42	2	32	328	0.57 [0.45, 0.68]	0.99 [0.98, 1.00]



Test 25. Xpert MTB/RIF, induced sputum, 5 to 14, culture

Xpert MTB/RIF, induced sputum, 5 to 14, culture

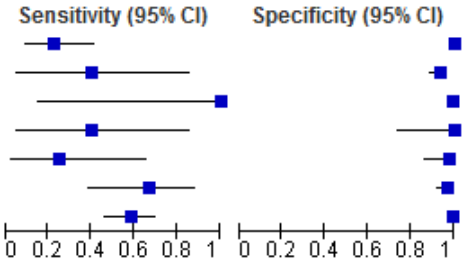
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Nicol 2011	7	0	0	24	1.00 [0.59, 1.00]	1.00 [0.86, 1.00]
Rachow 2012	11	2	6	52	0.65 [0.38, 0.86]	0.96 [0.87, 1.00]
Sekadde 2013	17	3	2	71	0.89 [0.67, 0.99]	0.96 [0.89, 0.99]
Zar 2012	10	0	3	201	0.77 [0.46, 0.95]	1.00 [0.98, 1.00]



Test 26. Xpert MTB/RIF, induced sputum, 0 to 4 years, culture

Xpert MTB/RIF, induced sputum, 0 to 4 years, culture

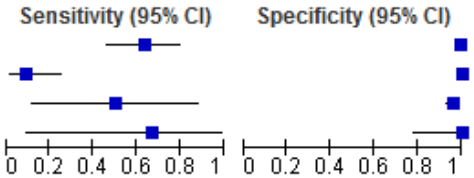
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bunyasi 2015	7	0	24	908	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nicol 2011	2	0	3	12	0.40 [0.05, 0.85]	1.00 [0.74, 1.00]
Rachow 2012	2	1	6	37	0.25 [0.03, 0.65]	0.97 [0.86, 1.00]
Sekadde 2013	10	4	5	123	0.67 [0.38, 0.88]	0.97 [0.92, 0.99]
Zar 2012	45	2	32	328	0.58 [0.47, 0.70]	0.99 [0.98, 1.00]



Test 27. Xpert MTB/RIF, gastric aspirate specimen, 0 to 4 years, culture

Xpert MTB/RIF, gastric aspirate specimen, 0 to 4 years, culture

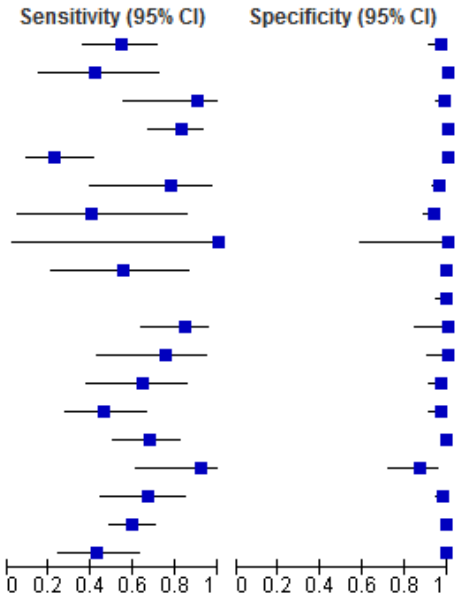
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	23	2	13	590	0.64 [0.46, 0.79]	1.00 [0.99, 1.00]
Bunyasi 2015	3	1	29	902	0.09 [0.02, 0.25]	1.00 [0.99, 1.00]
Chisti 2014	3	8	3	200	0.50 [0.12, 0.88]	0.96 [0.93, 0.98]
Nhu 2013	2	0	1	15	0.67 [0.09, 0.99]	1.00 [0.78, 1.00]



Test 28. Xpert MTB/RIF, sputum, culture, high tuberculosis burden, yes

Xpert MTB/RIF, sputum, culture, high tuberculosis burden, yes

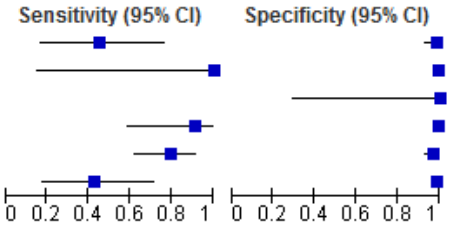
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	19	3	16	96	0.54 [0.37, 0.71]	0.97 [0.91, 0.99]
Bacha 2017	5	0	7	252	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]
Bates 2013	9	2	1	130	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Brent 2017	33	0	7	1064	0.82 [0.67, 0.93]	1.00 [1.00, 1.00]
Bunyasi 2015	7	0	24	908	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
Das 2019	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
Gous 2015	5	3	4	333	0.56 [0.21, 0.86]	0.99 [0.97, 1.00]
Hanrahan 2018	0	1	0	105	Not estimable	0.99 [0.95, 1.00]
Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Nicol 2013	11	3	6	95	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]
Rachow 2012	13	3	15	98	0.46 [0.28, 0.66]	0.97 [0.92, 0.99]
Reither 2015	25	3	12	315	0.68 [0.50, 0.82]	0.99 [0.97, 1.00]
Singh M 2016	11	5	1	33	0.92 [0.62, 1.00]	0.87 [0.72, 0.96]
Walters 2017a	16	6	8	240	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]
Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 29. Xpert MTB/RIF, sputum, culture, high tuberculosis burden, no

Xpert MTB/RIF, sputum, culture, high tuberculosis burden, no

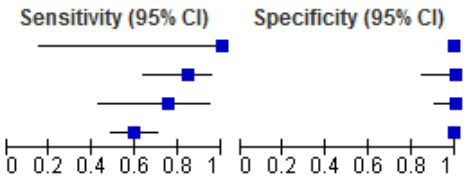
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Atwebembeire 2016	5	1	6	73	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Malbruny 2011	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Orikiriza 2018	10	3	1	325	0.91 [0.59, 1.00]	0.99 [0.97, 1.00]
Sekadde 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
Togun 2015	6	6	8	487	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]



Test 30. Xpert MTB/RIF, sputum, inpatients, culture

Xpert MTB/RIF, sputum, inpatients, culture

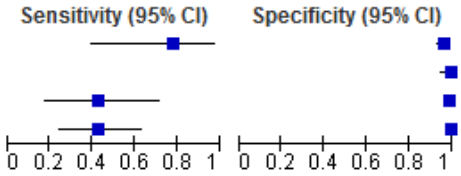
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]



Test 31. Xpert MTB/RIF, sputum, outpatients, culture

Xpert MTB/RIF, sputum, outpatients, culture

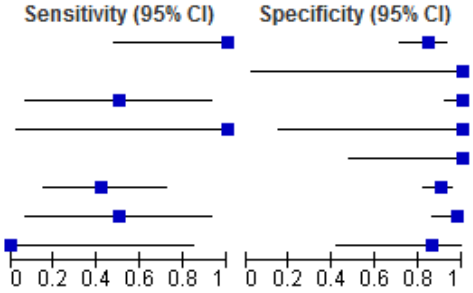
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Hanrahan 2018	0	1	0	105	Not estimable	0.99 [0.95, 1.00]
Togun 2015	6	6	8	487	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 32. Xpert MTB/RIF, CSF, culture

Xpert MTB/RIF, CSF, culture

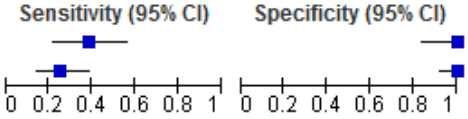
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bhatia 2016	5	8	0	42	1.00 [0.48, 1.00]	0.84 [0.71, 0.93]
Causse 2011	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Das 2019	2	0	2	47	0.50 [0.07, 0.93]	1.00 [0.92, 1.00]
Malbruny 2011	1	0	0	2	1.00 [0.03, 1.00]	1.00 [0.16, 1.00]
Nhu 2013	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Solomons 2015	5	9	7	80	0.42 [0.15, 0.72]	0.90 [0.82, 0.95]
Tortoli 2012	2	1	2	38	0.50 [0.07, 0.93]	0.97 [0.87, 1.00]
Vadwai 2011	0	1	2	6	0.00 [0.00, 0.84]	0.86 [0.42, 1.00]



Test 33. Xpert MTB/RIF, CSF, composite reference standard

Xpert MTB/RIF, CSF, composite reference standard

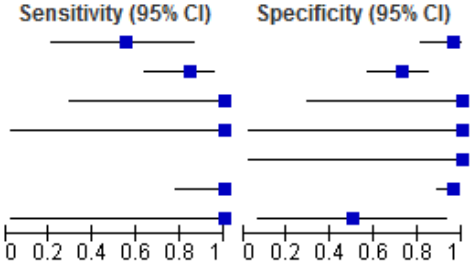
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bhatia 2016	13	0	21	21	0.38 [0.22, 0.56]	1.00 [0.84, 1.00]
Solomons 2015	14	0	41	45	0.25 [0.15, 0.39]	1.00 [0.92, 1.00]



Test 34. Xpert MTB/RIF, lymph node specimen, culture

Xpert MTB/RIF, lymph node specimen, culture

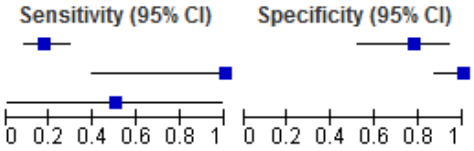
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bholla 2016	5	1	4	26	0.56 [0.21, 0.86]	0.96 [0.81, 1.00]
Coetzee 2014	21	13	4	34	0.84 [0.64, 0.95]	0.72 [0.57, 0.84]
Das 2019	3	0	0	3	1.00 [0.29, 1.00]	1.00 [0.29, 1.00]
Ligthelm 2011	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Malbruny 2011	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Tortoli 2012	15	3	0	71	1.00 [0.78, 1.00]	0.96 [0.89, 0.99]
Vadwai 2011	1	2	0	2	1.00 [0.03, 1.00]	0.50 [0.07, 0.93]



Test 35. Xpert MTB/RIF, lymph node specimen, composite reference standard

Xpert MTB/RIF, lymph node specimen, composite reference standard

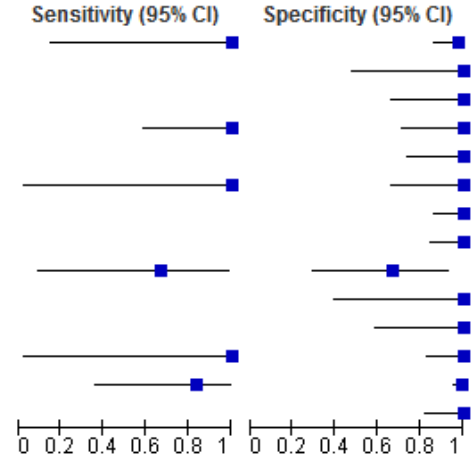
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bholla 2016	10	4	47	14	0.18 [0.09, 0.30]	0.78 [0.52, 0.94]
Kim 2015	4	0	0	26	1.00 [0.40, 1.00]	1.00 [0.87, 1.00]
Ligthelm 2011	1	0	1	0	0.50 [0.01, 0.99]	Not estimable



Test 36. Xpert MTB/RIF, rifampicin resistance, any specimen

Xpert MTB/RIF, rifampicin resistance, any specimen

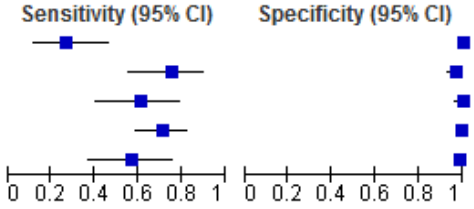
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	2	1	0	38	1.00 [0.16, 1.00]	0.97 [0.87, 1.00]
Bholla 2016	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Chipinduro 2017	0	0	0	9	Not estimable	1.00 [0.66, 1.00]
Das 2019	7	0	0	11	1.00 [0.59, 1.00]	1.00 [0.72, 1.00]
Malbruny 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Pang 2014	1	0	0	9	1.00 [0.03, 1.00]	1.00 [0.66, 1.00]
Rachow 2012	0	0	0	25	Not estimable	1.00 [0.86, 1.00]
Reither 2015	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Saini 2018	2	3	1	6	0.67 [0.09, 0.99]	0.67 [0.30, 0.93]
Tortoli 2012	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Walters 2014	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Yin 2014	1	0	0	20	1.00 [0.03, 1.00]	1.00 [0.83, 1.00]
Zar 2012	5	1	1	114	0.83 [0.36, 1.00]	0.99 [0.95, 1.00]
Zar 2013	0	0	0	19	Not estimable	1.00 [0.82, 1.00]



Test 37. Xpert MTB/RIF, sputum, multiple tests, culture

Xpert MTB/RIF, sputum, multiple tests, culture

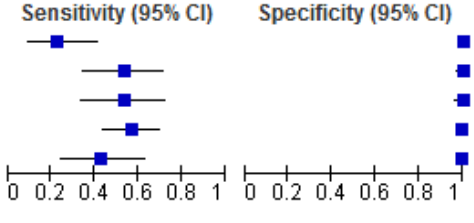
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bunyasi 2015	8	0	22	893	0.27 [0.12, 0.46]	1.00 [1.00, 1.00]
Rachow 2012	21	4	7	132	0.75 [0.55, 0.89]	0.97 [0.93, 0.99]
Sabi 2018	17	0	11	105	0.61 [0.41, 0.78]	1.00 [0.97, 1.00]
Zar 2012	45	3	18	330	0.71 [0.59, 0.82]	0.99 [0.97, 1.00]
Zar 2013	16	3	12	278	0.57 [0.37, 0.76]	0.99 [0.97, 1.00]



Test 38. Xpert MTB/RIF, sputum, initial test, culture

Xpert MTB/RIF, sputum, initial test, culture

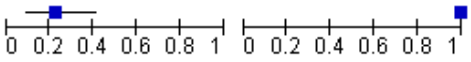
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bunyasi 2015	7	0	24	908	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Rachow 2012	16	0	14	132	0.53 [0.34, 0.72]	1.00 [0.97, 1.00]
Sabi 2018	15	0	13	105	0.54 [0.34, 0.72]	1.00 [0.97, 1.00]
Zar 2012	36	1	27	332	0.57 [0.44, 0.70]	1.00 [0.98, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 39. Xpert MTB/RIF, gastric aspirate specimen, multiple tests, culture

Xpert MTB/RIF, gastric aspirate specimen, multiple tests, culture

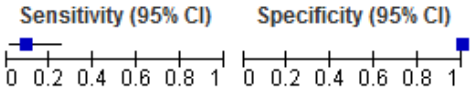
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bunyasi 2015	7	5	24	885	0.23 [0.10, 0.41]	0.99 [0.99, 1.00]		



Test 40. Xpert MTB/RIF, gastric aspirate specimen, initial test, culture

Xpert MTB/RIF, gastric aspirate specimen, initial test, culture

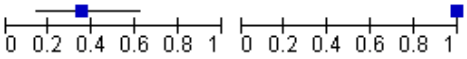
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bunyasi 2015	3	1	29	902	0.09 [0.02, 0.25]	1.00 [0.99, 1.00]		



Test 41. Xpert MTB/RIF, stool, multiple tests, culture

Xpert MTB/RIF, stool, multiple tests, culture

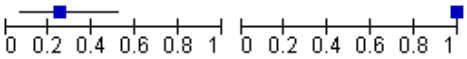
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Walters 2018a	6	1	11	229	0.35 [0.14, 0.62]	1.00 [0.98, 1.00]		



Test 42. Xpert MTB/RIF, stool, initial test, culture

Xpert MTB/RIF, stool, initial test, culture

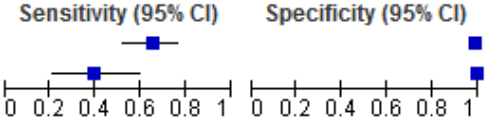
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Walters 2018a	4	1	12	219	0.25 [0.07, 0.52]	1.00 [0.97, 1.00]		



Test 43. Xpert MTB/RIF, nasopharyngeal aspirate, multiple tests, culture

Xpert MTB/RIF, nasopharyngeal aspirate, multiple tests, culture

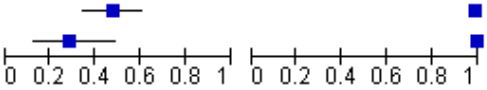
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2012	41	6	22	327	0.65 [0.52, 0.77]	0.98 [0.96, 0.99]		
Zar 2013	11	2	17	279	0.39 [0.22, 0.59]	0.99 [0.97, 1.00]		



Test 44. Xpert MTB/RIF, nasopharyngeal aspirate, initial test, culture

Xpert MTB/RIF, nasopharyngeal aspirate, initial test, culture

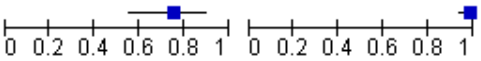
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2012	30	4	33	329	0.48 [0.35, 0.61]	0.99 [0.97, 1.00]		
Zar 2013	8	1	20	280	0.29 [0.13, 0.49]	1.00 [0.98, 1.00]		



Test 45. Xpert Ultra, sputum, multiple tests, culture

Xpert Ultra, sputum, multiple tests, culture

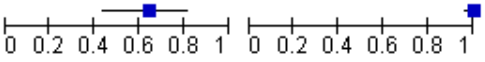
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Sabi 2018	21	2	7	105	0.75 [0.55, 0.89]	0.98 [0.93, 1.00]		



Test 46. Xpert Ultra, sputum, initial test, culture

Xpert Ultra, sputum, initial test, culture

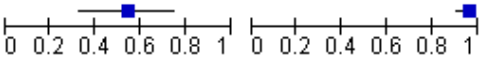
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Sabi 2018	18	0	10	107	0.64 [0.44, 0.81]	1.00 [0.97, 1.00]		



Test 47. Xpert Ultra, nasopharyngeal aspirate, multiple tests, culture

Xpert Ultra, nasopharyngeal aspirate, multiple tests, culture

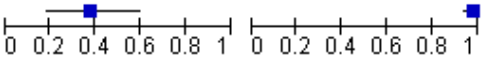
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2019	13	4	11	102	0.54 [0.33, 0.74]	0.96 [0.91, 0.99]		



Test 48. Xpert Ultra, nasopharyngeal aspirate, initial test, culture

Xpert Ultra, nasopharyngeal aspirate, initial test, culture

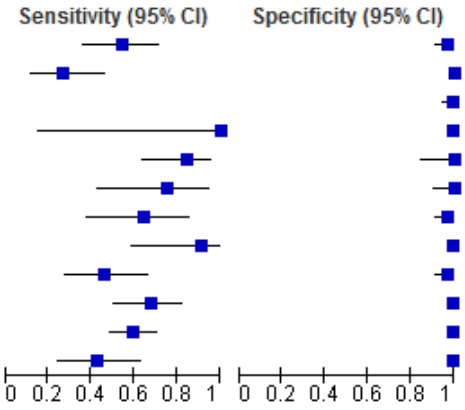
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2019	9	2	15	104	0.38 [0.19, 0.59]	0.98 [0.93, 1.00]		



Test 49. Xpert MTB/RIF, sputum, multiple cultures

Xpert MTB/RIF, sputum, multiple cultures

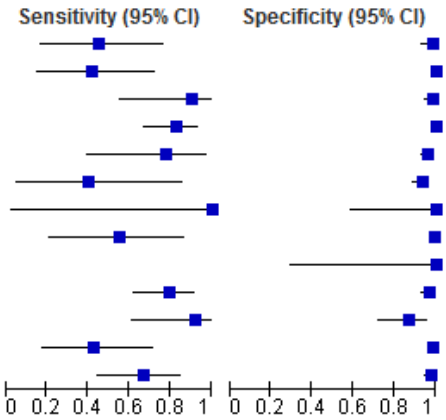
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anderson 2014	19	3	16	96	0.54 [0.37, 0.71]	0.97 [0.91, 0.99]
Bunyasi 2015	8	0	22	893	0.27 [0.12, 0.46]	1.00 [1.00, 1.00]
Hanrahan 2018	0	1	0	105	Not estimable	0.99 [0.95, 1.00]
LaCourse 2014	2	1	0	298	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Nicol 2013	11	3	6	95	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]
Orikiriza 2018	10	3	1	325	0.91 [0.59, 1.00]	0.99 [0.97, 1.00]
Rachow 2012	13	3	15	98	0.46 [0.28, 0.66]	0.97 [0.92, 0.99]
Reither 2015	25	3	12	315	0.68 [0.50, 0.82]	0.99 [0.97, 1.00]
Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 50. Xpert MTB/RIF, sputum, single culture

Xpert MTB/RIF, sputum, single culture

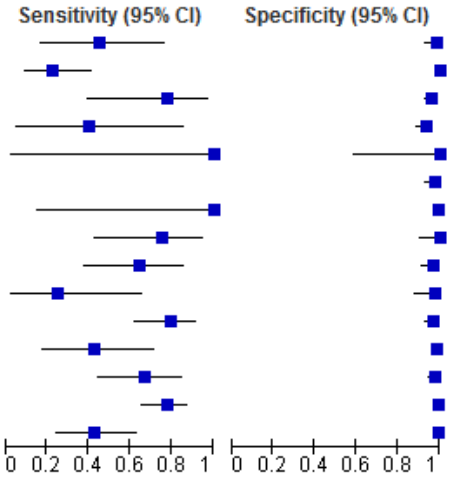
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Atwebembeire 2016	5	1	6	73	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]
Bacha 2017	5	0	7	252	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]
Bates 2013	9	2	1	130	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Brent 2017	33	0	7	1064	0.82 [0.67, 0.93]	1.00 [1.00, 1.00]
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
Das 2019	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
Gous 2015	5	3	4	333	0.56 [0.21, 0.86]	0.99 [0.97, 1.00]
Malbruny 2011	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Sekadde 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
Singh M 2016	11	5	1	33	0.92 [0.62, 1.00]	0.87 [0.72, 0.96]
Togun 2015	6	6	8	487	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Walters 2017a	16	6	8	240	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]



Test 51. Xpert MTB/RIF, induced sputum, culture

Xpert MTB/RIF, induced sputum, culture

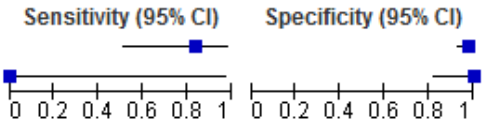
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Atwebembeire 2016	5	1	6	73	0.45 [0.17, 0.77]	0.99 [0.93, 1.00]
Bunyasi 2015	7	0	24	908	0.23 [0.10, 0.41]	1.00 [1.00, 1.00]
Chipinduro 2017	7	8	2	201	0.78 [0.40, 0.97]	0.96 [0.93, 0.98]
Chisti 2014	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
Das 2019	1	0	0	7	1.00 [0.03, 1.00]	1.00 [0.59, 1.00]
Hanrahan 2018	0	2	0	92	Not estimable	0.98 [0.93, 1.00]
LaCourse 2014	2	1	0	297	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
Nicol 2013	11	3	6	95	0.65 [0.38, 0.86]	0.97 [0.91, 0.99]
Rachow 2012	2	1	6	42	0.25 [0.03, 0.65]	0.98 [0.88, 1.00]
Sekadde 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
Togun 2015	6	6	8	487	0.43 [0.18, 0.71]	0.99 [0.97, 1.00]
Walters 2017a	16	6	8	240	0.67 [0.45, 0.84]	0.98 [0.95, 0.99]
Zar 2012	52	2	15	385	0.78 [0.66, 0.87]	0.99 [0.98, 1.00]
Zar 2013	12	1	16	280	0.43 [0.24, 0.63]	1.00 [0.98, 1.00]



Test 52. Xpert MTB/RIF, gastric aspirate specimen, 5 to 14, culture

Xpert MTB/RIF, gastric aspirate specimen, 5 to 14, culture

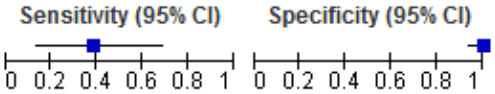
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bates 2013	10	3	2	119	0.83 [0.52, 0.98]	0.98 [0.93, 0.99]
Nhu 2013	0	0	1	19	0.00 [0.00, 0.97]	1.00 [0.82, 1.00]



Test 53. Xpert MTB/RIF, nasopharyngeal aspirate, 5 to 14, culture

Xpert MTB/RIF, nasopharyngeal aspirate, 5 to 14, culture

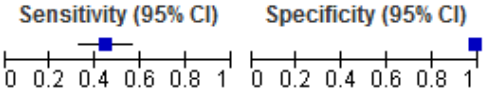
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2012	5	0	8	57	0.38 [0.14, 0.68]	1.00 [0.94, 1.00]



Test 54. Xpert MTB/RIF, nasopharyngeal aspirate, 0 to 4, culture

Xpert MTB/RIF, nasopharyngeal aspirate, 0 to 4, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zar 2012	33	5	41	325	0.45 [0.33, 0.57]	0.98 [0.96, 1.00]



ADDITIONAL TABLES

Table 1. Key characteristics of included studies

Study	Index test	Reference standard	Study design	HIV status	Clinical setting	High TB burden	Specimens	Uninterpretable results for tuberculosis detection
Anderson 2014	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Sputum	NR
Andriyoko 2019	Xpert MTB/RIF	Culture	Cross-sectional	NR	NR	Yes	Gastric aspirate specimen, stool, sputum	6/40 (15%) stool, induced sputum or gastric aspirate specimen 1/30 (3%)
Atwebembeire 2016	Xpert MTB/RIF	Culture	Cross-sectional	Both	NR	No	Sputum	NR
Bacha 2017	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Sputum	3/455 (0.6%)
Bates 2013	Xpert MTB/RIF	Culture	Cross-sectional	Both	Inpatient	Yes	Sputum, gastric aspirate specimen	17/930 (1.8%)
Bhatia 2016	Xpert MTB/RIF	Culture, Composite	Cross-sectional	NR	Inpatient	Yes	Cerebrospinal fluid	NR
Bholla 2016	Xpert MTB/RIF	Culture	Cohort	Both	NR	Yes	Lymph node specimen	0/70 (0%)
Brent 2017	Xpert MTB/RIF	Culture, Composite	Cohort	Both	NR	Yes	Sputum	NR
Bunyasi 2015	Xpert MTB/RIF	Culture	Randomized trial	HIV-	Inpatient	Yes	Sputum, gastric aspirate specimen	47/4856 (0.9%)
Causse 2011	Xpert MTB/RIF	Culture	Cross-sectional	HIV-	Laboratory	No	Gastric aspirate specimen, cerebrospinal fluid	NR
Chipinduro 2017	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Outpatient	Yes	Sputum, stool	1/218 (0.4%) induced spu-

Table 1. Key characteristics of included studies *(Continued)*

								tum, 0/218 stool
Chisti 2014	Xpert MTB/RIF	Culture, Composite	Cross-sectional	NR	Inpatient	Yes	Gastric aspirate specimen, sputum	NR
Coetzee 2014	Xpert MTB/RIF	Culture	Cross-sectional	Both	Both	Yes	Lymph node	1/110 (0.9%)
Das 2019	Xpert MTB/RIF	Culture	Cross-sectional	Both	Both	Yes	Gastric aspirate specimen, cerebrospinal fluid, lymph node, sputum	2/181 (1%)
Gous 2015	Xpert MTB/RIF	Culture	Cross-sectional	NR	NR	Yes	Sputum	27/467 (5.6%)
Hanrahan 2018	Xpert MTB/RIF	Culture	Cohort	Both	Outpatient	Yes	Gastric aspirate specimen, nasopharyngeal specimen, sputum, stool	15/114 (13%) stool, 1/57 (1.7%) gastric, 1/103 (.9%) IS
Hasan 2017	Xpert MTB/RIF	Culture, Composite	Cross-sectional	HIV-	Both	Yes	Gastric aspirate specimen, stool, sputum	NR
Kasa Tom 2018	Xpert MTB/RIF	Composite	Cohort	Both	Inpatient	Yes	Gastric aspirate specimen, sputum	NR
Kim 2015	Xpert MTB/RIF	Culture	Cross-sectional	NR	Inpatient	No	Lymph node specimen	NR
LaCourse 2014	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Inpatient	No	Sputum	0/300 (0%)
LaCourse 2018	Xpert MTB/RIF	Culture, Composite	Cohort	HIV+	Inpatient	Yes	Gastric aspirate specimen, sputum, stool	2/150 (1.3%)
Ligthelm 2011	Xpert MTB/RIF	Culture	Cross-sectional	NR	Both	Yes	Lymph node specimen	0/2 (0%)
Malbruny 2011	Xpert MTB/RIF	Culture	Cross-sectional	NR	Laboratory	No	Gastric aspirate specimen, cerebrospinal fluid, lymph node, sputum	NR

Table 1. Key characteristics of included studies *(Continued)*

Marcy 2016	Xpert MTB/RIF	Culture	Cohort	HIV+	NR	Yes	Gastric aspirate specimen, nasopharyngeal specimen, sputum, stool	NR
Moussa 2016	Xpert MTB/RIF	Culture, Composite	Cohort	HIV-	NR	No	Sputum, stool	1/230 (.4%)
Myo 2018	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Inpatient	Yes	Gastric aspirate specimen	4/231 (1.7%)
Nhu 2013	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Inpatient	Yes	Gastric aspirate specimen, sputum, cerebrospinal fluid	NR
Nicol 2011	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Inpatient	Yes	Sputum	NR
Nicol 2013	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Sputum, stool	NR
Nicol 2018	Xpert MTB/RIF and Xpert Ultra	Culture, Composite	Cohort	Both	Inpatient	Yes	Sputum	NR
Orikiriza 2018	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	No	Sputum, stool	2/357 (0.5%) sputum, 1/64 (1.5%) stool
Pang 2014	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Unk/NR	Inpatient	Yes	Gastric aspirate specimen	NR
Rachow 2012	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Sputum	NR
Reither 2015	Xpert MTB/RIF	Culture, Composite	Cohort	Both	NR	Yes	Sputum	NR
Sabi 2018	Xpert MTB/RIF and Xpert Ultra	Culture, Composite	Cohort	Both	Both	Yes	Sputum	3/520 (0.5%)
Saini 2018	Xpert MTB/RIF	Culture, Composite	Cross-sectional	HIV-	Inpatient	Yes	Bronchoalveolar lavage	NR
Sekadde 2013	Xpert MTB/RIF	Culture	Cross-sectional	Both	Both	No	Sputum	2/250 (0.8%)

Table 1. Key characteristics of included studies *(Continued)*

Singh M 2016	Xpert MTB/RIF	Culture, Composite	Cross-sectional	NR	Inpatient	Yes	Gastric aspirate specimen, sputum	NR
Solomons 2015	Xpert MTB/RIF	Culture, Composite	Cross-sectional	Both	Inpatient	Yes	Cerebrospinal fluid	NR
Togun 2015	Xpert MTB/RIF	Culture, Composite	Cross-sectional	HIV-	Outpatient	No	Sputum	NR
Tortoli 2012	Xpert MTB/RIF	Culture	Cross-sectional	NR	Laboratory	No	Gastric aspirate specimen, cerebrospinal fluid, lymph node specimen	0/306
Vadwai 2011	Xpert MTB/RIF	Culture	Cross-sectional	Both	Both	Yes	Cerebrospinal fluid	NR
Walters 2014	Xpert MTB/RIF	Culture	Cross-sectional	Both	Inpatient	Yes	Bronchoalveolar lavage	NR
Walters 2017a	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Gastric aspirate specimen, sputum, stool	28/379 (7%)
Walters 2018a	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Both	Yes	Gastric aspirate specimen, sputum, stool	12/259 (5%) stool, 8/259 (3%) respiratory
Yin 2014	Xpert MTB/RIF	Culture	Cross-sectional	NR	Inpatient	Yes	Bronchoalveolar lavage	4/255 (1.6%)
Zar 2012	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Inpatient	Yes	Nasopharyngeal specimen, sputum	NR
Zar 2013	Xpert MTB/RIF	Culture, Composite	Cohort	Both	Outpatient	Yes	Nasopharyngeal specimen, sputum	12/1754 (0.6%)
Zar 2019	Xpert MTB/RIF and Xpert Ultra	Culture, Composite	Cohort	Both	Inpatient	Yes	Nasopharyngeal specimen, sputum	NR

IS: induced sputum; NR: not reported; TB: tuberculosis.

Table 2. Diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis and rifampicin resistance in children

Test, analysis group	Reference standard	Studies	Number of children (TB cases)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)[a]	Negative predictive value % (95% CI)[a]
Xpert MTB/RIF, sputum	Culture	23	6703 (493)	64.6 (55.3 to 72.9)	99.0 (98.1 to 99.5)	88.2 (79.6 to 93.5)	96.2 (95.1 to 97.0)
Xpert MTB/RIF, sputum	Composite	16	4379 (1541)	19.7 (12.1 to 30.4)	100 (99.8 to 100)	98.4 (89.2 to 99.8)	91.8 (90.9 to 92.6)
Xpert Ultra, sputum	Culture	3	697 (136)	72.8 (64.7 to 79.6)	97.5 (95.8 to 98.5)	76.4 (65.6 to 84.6)	97.7 (95.9 to 97.7)
Xpert Ultra, sputum	Composite	3	753 (498)	23.5 (20.0 to 27.4)	99.2 (96.9 to 99.8)	76.9 (45.3 to 93.0)	92.1 (91.7 to 92.5)
Xpert MTB/RIF, gastric aspirate specimen	Culture	14	3482 (273)	73.0 (52.9 to 86.7)	98.1 (95.5 to 99.2)	81.0 (65.5 to 90.6)	97.0 (94.5 to 98.4)
Xpert MTB/RIF, gastric aspirate specimen	Composite	6	933 (461)	31.7 (20.2 to 46.0)	99.7 (97.1 to 100)	91.7 (58.3 to 98.9)	92.9 (91.6 to 94.0)
Xpert MTB/RIF, stool specimen	Culture	11	1592 (174)	61.5 (44.1 to 76.4)	98.5 (97.0 to 99.2)	81.7 (72.2 to 88.5)	95.8 (93.8 to 97.3)
Xpert MTB/RIF, stool specimen	Composite	10	1739 (879)	16.3 (8.4 to 29.2)	99.7 (97.8 to 100)	87.4 (42.8 to 98.5)	91.5 (90.5 to 92.4)
Xpert MTB/RIF, nasopharyngeal specimen	Culture	4	1125 (144)	45.7 (27.6 to 65.1)	99.6 (98.9 to 99.8)	92.6 (81.1 to 97.3)	94.3 (92.0 to 95.9)
Xpert Ultra, nasopharyngeal specimen	Culture	1	195 (35)	45.7 (28.9 to 63.3)	97.5 (93.7 to 99.3)	67.0 (42.0 to 85.1)	94.1 (92.2 to 95.6)
Xpert MTB/RIF, sputum, smear-positive[b]	Culture	11	91 (88)	97.8 (91.6 to 99.4)	–	–	–
Xpert MTB/RIF, sputum, smear-negative	Culture	12	3118 (184)	58.9 (45.6 to 71.0)	99.1 (97.1 to 99.7)	88.4 (68.8 to 96.3)	95.6 (94.0 to 96.8)
Xpert MTB/RIF, sputum, HIV-positive	Culture	10	642 (88)	72.2 (59.9 to 81.8)	99.4 (97.2 to 99.9)	93.2 (74.0 to 98.5)	97.0 (95.5 to 97.9)
Xpert MTB/RIF, sputum, HIV-negative	Culture	12	2784 (224)	54.3 (43.5 to 64.7)	99.3 (98.1 to 99.7)	89.7 (80.5 to 94.9)	95.1 (93.9 to 96.2)

Table 2. Diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis and rifampicin resistance in children *(Continued)*

Xpert MTB/RIF, gastric aspirate specimen, HIV-positive	Culture	3	634 (50)	73.3 (54.9 to 86.1)	98.5 (97.1 to 99.2)	84.1 (72.7 to 91.3)	97.1 (93.8 to 98.4)
Xpert MTB/RIF, stool specimen, HIV-positive	Culture	4	526 (53)	69.8 (56.3 to 80.6)	98.6 (96.1 to 99.5)	84.7 (66.2 to 94.0)	96.7 (95.1 to 97.8)
Xpert MTB/RIF, rifampicin resistance	Culture-DST, MTBDR*plus*	6	223 (20)	90.0 (67.6 to 97.5)	98.3 (87.7 to 99.8)	85.7 (42.7 to 98.0)	98.9 (95.9 to 99.7)

CI: confidence interval; DST: drug susceptibility testing; MTBDR*plus*: molecular assay for detection of *Mycobacterium tuberculosis* and drug resistance; TB: tuberculosis.
[a]Predictive values were determined at a pre-test probability of 10%.
[b]We performed a univariate meta-analysis for this analysis group because in many studies, few or zero false-positive and true-negative values were reported.

Table 3. Direct comparison of Xpert MTB/RIF and Xpert Ultra, sputum specimen (culture reference standard)

Test, analysis group	Studies	Number of children (cases)	Sensitivity % (95% CI)	Specificity % (95% CI)
Xpert Ultra	3	697 (146)	70.5 (62.7 to 77.4)	97.3 (95.5 to 98.4)
Xpert MTB/RIF	3	609 (136)	63.2 (54.8 to 70.9)	99.2 (97.8 to 99.7)
Absolute difference			7.31 (-3.66 to 18.3), P = 0.19	-1.88 (-3.47 to -0.29), P = 0.02

CI: confidence interval.
Sensitivity and specificity estimates were determined with respect to culture.

Table 4. Effects of potential sources of heterogeneity on the accuracy of Xpert MTB/RIF accuracy for pulmonary tuberculosis

Test, analysis group	Studies	Number of children (cases)	Sensitivity % (95% CI)	Specificity % (95% CI)
Age group				
Induced sputum, 5 to 14 years	5	627 (65)	80.5 (66.9 to 89.4)	98.2 (94.4 to 99.4)
Induced sputum, 0 to 4 years	7	2062 (143)	48.6 (32.5 to 65.0)	99.4 (96.7 to 99.9)
Absolute difference			31.9 (11.7 to 52.2), P = 0.002	-1.15 (-3.49 to 1.20), P = 0.34
Gastric aspirate specimen, 0 to 4 years	4	1795 (77)	43.0 (16.2 to 74.6)	99.5 (97.0 to 99.9)
High tuberculosis burden				
Yes	18	5162 (422)	63.8 (53.5 to 73.0)	99.1 (97.9 to 99.6)
No	5	1466 (72)	70.2 (46.9 to 86.3)	98.8 (97.6 to 99.4)
Absolute difference			-6.42 (-29.2 to 16.3), P = 0.58	0.35 (-0.79 to 1.49), P = 0.55
High TB/HIV burden				
Yes	19	5824 (415)	65.7 (55.0 to 75.1)	99.2 (98.3 to 99.7)
No	4	879 (79)	59.5 (39.6 to 76.7)	97.4 (93.8 to 98.9)
Absolute difference			6.26 (-15.7 to 28.2), P = 0.58	1.88 (-0.51 to 4.26), P = 0.12
Cultures used to verify tuberculosis				
Multiple	11	3174 (312)	61.0 (48.9 to 71.9)	99.3 (98.4 to 99.7)
Single	12	3439 (181)	69.1 (56.6 to 79.3)	98.6 (96.5 to 99.5)
Absolute difference			-8.05 (-24.4 to 8.35), P = 0.34	0.67 (-0.74 to 2.09), P = 0.35

CI: confidence interval; TB: tuberculosis.
Sensitivity and specificity estimates were determined with respect to culture.

Table 5. Diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for tuberculous meningitis and lymph node tuberculosis

Test, analysis group	Reference standard	Studies	Number of children (TB cases)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)[a]	Negative predictive value % (95% CI)[a]
Xpert MTB/RIF, CSF	Culture	6	262 (28)	54.0 (27.8 to 78.2)	93.8 (84.5 to 97.6)	49.1 (26.8 to 71.7)	94.8 (91.1 to 97.1)
Xpert MTB/RIF, CSF[b]	Composite	3	160 (94)	–	–	–	–
Xpert MTB/RIF, Lymph node	Culture	6	210 (54)	90.4 (55.7 to 98.6)	89.8 (71.5 to 96.8)	49.6 (23.7 to 75.7)	98.8 (93.1 to 99.8)
Xpert MTB/RIF, Lymph node[b]	Composite	3	107 (63)	–	–	–	–

CI: confidence interval; CSF: cerebrospinal fluid; TB: tuberculosis.
[a]Predictive values were determined at a pre-test probability of 10%.
[b]We did not perform a meta-analysis owing to limited data.

Table 6. Diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis in children, comparison of repeated testing versus first test (culture reference standard)

Test, analysis group	Studies	Number of children (TB cases)	Sensitivity %(95% CI)	Specificity %(95% CI)
More than 1 Xpert MTB/RIF, sputum	5	1925 (177)	59.1 (43.0 to 73.4)	99.5 (97.7 to 99.9)
One Xpert MTB/RIF, sputum	5	1939 (180)	46.3 (35.0 to 57.9)	99.9 (99.5 to 100)
Absolute difference			12.8 (-6.78 to 32.3), P = 0.20	-0.34 (-1.09 to 0.41), P = 0.37
More than 1 Xpert Ultra, sputum	1	135 (28)	75.0 (55.1 to 89.3)	98.1 (93.4 to 99.8)
One Xpert Ultra, sputum	1	135 (28)	64.3 (44.1 to 81.4)	100 (96.6 to 100)
Absolute difference			10.7 (-13.2 to 34.6), P = 0.38	-1.87 (-4.44 to 0.70), P = 0.16
More than 1 Xpert MTB/RIF, gastric aspirate specimen	1	921 (31)	22.6 (9.59 to 41.1)	99.4 (98.7 to 99.8)
One Xpert MTB/RIF, gastric aspirate specimen	1	935 (32)	9.38 (1.98 to 25.0)	99.9 (99.4 to 100)
Absolute difference			13.2 (-4.64 to 31.1), P = 0.15	-0.45 (-0.99 to 0.09), P = 0.10
More than 1 Xpert MTB/RIF, stool specimen	1	247 (17)	35.3 (14.2 to 61.7)	99.6 (97.6 to 100)
One Xpert MTB/RIF, stool specimen	1	236 (16)	25.0 (7.27 to 52.4)	99.5 (97.5 to 100)
Absolute difference			10.3 (-20.8 to 41.4), P = 0.52	0.02 (-1.21 to 1.25), P = 0.97
More than 1 Xpert MTB/RIF, nasopharyngeal specimen	2	705 (91)	54.2 (36.1 to 71.3)	98.7 (97.4 to 99.3)
One Xpert MTB/RIF, nasopharyngeal specimen	2	705 (91)	40.7 (27.9 to 54.9)	99.2 (98.1 to 99.7)
Absolute difference			13.5 (-9.50 to 36.5), P = 0.25	-0.49 (-1.63 to 0.66), P = 0.40
More than 1 Xpert Ultra, nasopharyngeal specimen	1	130 (24)	54.2 (32.8 to 74.4)	96.2 (90.6 to 99.0)
One Xpert Ultra, nasopharyngeal specimen	1	130 (24)	37.5 (18.8 to 59.4)	98.1 (93.4 to 99.8)
Absolute difference			16.7 (-11.1 to 44.5), P = 0.25	-1.89 (-6.34 to 2.57), P = 0.41

CI: confidence interval; TB: tuberculosis.

Table 7. Sensitivity analyses for accuracy of Xpert MTB/RIF for detection of pulmonary tuberculosis, sputum specimen (culture reference standard)

Analysis	Studies	Number of children (TB cases)	Sensitivity % (95% CI)	Specificity % (95% CI)
Random or consecutive recruitment of participants	22	6485 (485)	64.0 (54.4 to 72.6)	99.1 (98.2 to 99.6)
Blinding of reference standard to index test results	18	5796 (454)	65.5 (55.3 to 74.4)	99.0 (98.0 to 99.5)
No pretreatment of participants	21	5877 (469)	64.2 (54.8 to 72.7)	99.1 (98.0 to 99.6)
Enrolled only children 0 to 14 years old	20	5950 (437)	65.5 (54.9 to 74.7)	99.1 (98.1 to 99.6)
Sputum only (excluding studies that also collected gastric aspirate specimen)	22	6653 (482)	63.0 (53.8 to 71.3)	99.2 (98.4 to 99.6)

CI: confidence interval; TB: tuberculosis.

APPENDICES

Appendix 1. Detailed search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 25, 2019>

Search Strategy:

Search Name: Cochrane Central Register of Controlled Trials

1 Mycobacterium tuberculosis/

2 Tuberculosis/ or "Tuberculosis, Multidrug-Resistant"/ or Extensively Drug-Resistant Tuberculosis/ or Tuberculosis, Pulmonary/ or Tuberculosis, Lymph Node/ or Tuberculosis, Meningeal/

3 (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ti. or (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ab.

4 ((extrapulmonary or lymph node* or mening* or pulmonary) and TB).ti. or ((extrapulmonary or lymph node* or mening* or pulmonary) and TB).ab.

5 1 or 2 or 3 or 4

6 Xpert*.ti. or Xpert*.ab.

7 (GeneXpert or cepheid).ti. or (GeneXpert or cepheid).ab.

8 (Xpert* and Ultra).mp.

9 (near* patient or near-patient).ti. or (near* patient or near-patient).ab.

10 6 or 7 or 8 or 9

11 5 and 10

12 (pediatric* or paediatric*).mp.

13 (child or children* or childhood or infan* or newborn or neonat* or toddler* or adolescen*).mp.

14 exp Child/ or exp Infant/ or Adolescent/ or exp Pediatrics/

15 12 or 13 or 14

16 11 and 15

20 19 and 16

Database: Embase 1947-Present, updated daily

Search Strategy:

1 Mycobacterium tuberculosis.mp. or Mycobacterium tuberculosis/

2 lung tuberculosis/ or extrapulmonary tuberculosis/ or extensively drug resistant tuberculosis/ or multidrug resistant tuberculosis/ or drug resistant tuberculosis/ or tuberculosis/

3 (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ti. or (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ab.

4 ((extrapulmonary or lymph node* or mening* or pulmonary) and TB).ti. or ((extrapulmonary or lymph node* or mening* or pulmonary) and TB).ab.

5 1 or 2 or 3 or 4

6 Xpert*.ti. or Xpert*.ab.

7 (GeneXpert or cepheid).ti. or (GeneXpert or cepheid).ab.

8 (Xpert* and Ultra).mp.

9 (near* patient or near-patient).ti. or (near* patient or near-patient).ab.

10 6 or 7 or 8 or 9

11 5 and 10

12 (pediatric* or paediatric*).mp.

13 (child or children* or childhood or infan* or newborn or neonat* or toddler* or adolescen*).mp.

14 child/

15 infant/

16 adolescent/

17 pediatrics/

18 12 or 13 or 14 or 15 or 16 or 17

19 11 and 18

Search Name: Cochrane Central Register of Controlled Trials

Issue 4 of 12, April 2019

ID Search

#1 mycobacterium tuberculosis

#2 MeSH descriptor: [Mycobacterium tuberculosis] explode all trees

#3 Tuberculosis or MDR-TB or XDR-TB or tuberculous

#4 MeSH descriptor: [Tuberculosis, Pulmonary] explode all trees

#5 MeSH descriptor: [Tuberculosis] explode all trees

#6 MeSH descriptor: [Extensively Drug-Resistant Tuberculosis] explode all trees

#7 MeSH descriptor: [Tuberculosis, Multidrug-Resistant] explode all trees

#8 MeSH descriptor: [Tuberculosis, Lymph Node] explode all trees

#9 MeSH descriptor: [Tuberculosis, Meningeal] explode all trees

#10 ((extrapulmonary or lymph node* or mening* or pulmonary) and TB)

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

#12 Xpert* or GeneXpert or cepheid

#13 (Xpert* and Ultra)

#14 (near* patient or near-patient)

#15 #12 or #13 or #14

#16 #11 and #15

#17 child or children* or childhood or infan* or newborn or neonat* or toddler* or adolescen*

#18 pediatric* or paediatric*

#19 #17 or #18

CINAHL (EBSCOHost)

Query

S9 S7 AND S8

S8 "(child or children* or childhood or infan* or newborn or neonat* or toddler* or adolescen*) OR (pediatric* or paediatric*)"

S7 S3 AND S6

S6 S4 OR S5

S5 "Xpert MTB/RIF"

S4 "(Xpert* or GeneXpert or cepheid) OR (Xpert* and Ultra) OR (near* patient or near-patient)"

S3 S1 OR S2

S2 "(XDR-TB or MDR-TB) OR extrapulmonary tuberculosis"

S1 (MH "Mycobacterium Tuberculosis") OR (MH "Tuberculosis, Multidrug-Resistant") OR (MH "Tuberculosis, Meningeal") OR (MH "Tuberculosis") OR "tuberculosis OR drug resistant tuberculosis OR Mycobacterium tuberculosis"

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

7 #6 AND #5

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

6 TOPIC: (child or children* or childhood or infan* or newborn or neonat* or toddler* or adolescen*) OR TOPIC: (pediatric* or paediatric*)

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

5 #4 AND #1

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

4 #3 OR #2

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

3 TOPIC: (Xpert* Ultra or Cepheid or near* patient)

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

2 TOPIC: (Xpert* or Xpert MTB RIF)

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

1 TOPIC: (Tuberculosis or MDR-TB or XDR-TB or tuberculous) OR TOPIC: (mycobacterium tuberculosis) OR TOPIC: (((extrapulmonary or lymph node* or mening* or pulmonary) and TB))

Indexes=SCI-EXPANDED, CPCI-S Time span=All years

SCOPUS (Elsevier)

(TITLE-ABS-KEY ((tuberculosis OR mdr-tb OR xdr-tb OR tuberculous) OR (mycobacterium AND tuberculosis) OR (((extrapulmonary OR lymph AND node* OR mening* OR pulmonary) AND tb)))) AND (TITLE-ABS-KEY ((xpert* OR xpert AND mtb AND rif) OR (xpert* AND ultra OR cepheid OR near* AND patient))) AND (TITLE-ABS-KEY ((child OR children* OR childhood OR infan* OR newborn OR neonat* OR toddler* OR adolescen*) OR (pediatric* OR paediatric*)))

ClinicalTrials.gov, WHO ICTRP, and ISRCTN Registry: tuberculosis and Xpert* and children

Appendix 2. Data extraction form

Diagnostic accuracy of Xpert in the diagnosis of child tuberculosis: data extraction form	
I. ID	
Study ID	First Name/Publication Year
First author	Name
Corresponding author	Name
Corresponding author email	Email
Was author contacted?	1 – Yes 2 – No If yes, dates(s)
If yes, author response?	
Study data	1 - Published 2 - In press 3 - Ongoing
Title	
Year (of publication)	YYYY or 9 – Not reported
Year study start date	YYYY or 9 – Not reported
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

(Continued)

	4 - Low and high income 5 - Other combination, describe
Country tuberculosis burden (WHO 2015)	1 - WHO tuberculosis high burden 2 - WHO tuberculosis/HIV high burden 3 - WHO MDR tuberculosis high burden 4 - WHO tuberculosis + MDR tuberculosis high burden 5 - WHO tuberculosis + HIV/tuberculosis high burden 6 - WHO tuberculosis + HIV/tuberculosis + MDR tuberculosis high burden 7 - Not a WHO high-burden country 8 - Both non-high-burden and high-burden countries included 9 - Other
Study design	1 – Randomized controlled trial 2 – Cross-sectional 3 – Cohort 4 – Other, specify 9 – Could not tell If other, describe:
Participant selection	1 – Consecutive 2 – Random 3 – Convenience 7 – Other 9 – Unknown/Not reported
Direction of study data collection	1 – Prospective 2 – Retrospective 9 – Unknown/Not reported
Inclusion criteria	1 – Broad 2 – Rigorous 9 – Unknown/Not reported
Inclusion criteria for presumptive tuberculosis	1 – Tuberculosis contact 2 – Cough 3 – Loss of weight 4 – Suggestive chest X-ray 5 – Immunological evidence of tuberculosis infection (TST/IGRA) 6 - Malnutrition 7 – HIV 8 - Other, describe 9 – Unknown/Not reported
Describe inclusion criteria as in study	
Number included after recruitment by inclusion and exclusion criteria	Enter number or 9 – Unknown/Not reported
Total number of children included in systematic review analysis	Enter number or 9 – Unknown/Not reported

(Continued)

Total number of specimens included in analysis with collection method	Enter number or 9 – Unknown/Not reported
Unit of analysis (Xpert)	1 – One specimen per patient 2 – Multiple specimens per patient 3 - Unknown number of specimens per patient 9 – Unknown/Not reported Describe as written in study, if unclear:
Did the study include patients with previous tuberculosis history?	1 – Yes 0 – No 9 – Unknown/Not reported
If so, what is the percentage?	Enter % and specify numerator/denominator
Target condition? Pulmonary tuberculosis?	1 - Yes 0 - No
Target condition? Rifampicin resistance?	1 - Yes 0 - No
Target condition? Lymph node tuberculosis?	1 - Yes 0 - No
Target condition? Tuberculous meningitis?	1 - Yes 0 - No
Comments about study design	
III. Patient characteristics and setting	
Description of study population (age, HIV info, etc.)	1 – All enrolled 2 – All analysed 9 – Unknown/Not reported
Age: median, mean, range by months	Enter number or 9 – Unknown/Not reported
Gender	##/total and % female
HIV status of participants	0 – HIV- 1 – HIV+ 2 – Both HIV+/- 9 – Unknown/Not reported
If HIV-positive participants included, what is the percentage?	% and specify numerator/denominator
Type of respiratory specimen included	1 – All expectorated 2 – All induced 3 – All bronchoalveolar lavage 4 – All gastric lavage 5 – Nasopharyngeal aspirate 6 - Stool 7 – Multiple types 8 – Other 9 – Unknown/Not reported If 7 or 8, describe types and record numbers:

(Continued)

Type of non-respiratory specimen	1 – Fine needle aspirate 2 – Lymph node biopsy 3 – Cerebrospinal fluid 4 – Multiple types 5 - Other 9 - Unknown/Not reported If 4 or 5, describe types and record numbers:
Were Xpert sample and culture obtained from same specimen?	1 – Yes 0 – No 9 – Unknown/Not reported
Number of cultures used to exclude tuberculosis	Describe
Information on smear microscopy: was it used?	1 – Yes 0 – No 9 – Unknown/Not reported
Type of microscopy used	1 – Ziehl-Neelsen 2 – Fluoresence microscopy 3 - Light emitting diode-based fluorescence microscopy 4 - Multiple, describe: 9 – Unknown/Not reported
Smear type	1 – Direct 2 – Concentrated (processed) 3 - Both direct and concentrated 9 – Unknown/Not reported
Data on culture performance provided?	# of contaminated culture/Total # cultures performed or 9 - Unknown/Not reported
Were patient-important outcomes evaluated? (time to diagnosis, time to treatment, others)	1 – Yes 2 – No 9 – Unknown/Not reported
Time to diagnosis?	Xpert: Culture: 9 – Unknown/Not reported Specify whether time from sample collection to diagnosis in lab or just turn-around time in lab
Time to treatment initiation	Xpert: Culture: 9 – Unknown/Not reported
Clinical setting, describe as written in the paper	1 – Outpatient 2 – Inpatient 3 – Both outpatient and inpatient 4 – Other, specify 5 – Laboratory based 9 – Unknown/Not reported Describe as in paper:
Laboratory services level	1 - Central (reference) 2 - Intermediate (regional) 3 - Peripheral (microscopy centre, provincial hospital) 4 – Research laboratory

(Continued)

	5 - Other, specify
Where were Xpert tests performed? (tests generally available at different laboratory levels, although tests may overlap) Peripheral: acid-fast bacilli (Ziehl-Neelsen, Auramine-rhodamine, Auramine-O staining) and Xpert MTB/RIF Intermediate: peripheral laboratory tests and culture on solid media and line probe assay (LPA) from smear-positive sputum Central: intermediate laboratory tests and culture on liquid media and DST (1st-line and 2nd-line anti-tuberculosis drugs) on solid or in liquid media and LPA on positive cultures and rapid speciation tests	1 - Central (reference) 2 - Intermediate (regional) 3 - Peripheral (microscopy centre, provincial hospital) 4 - Other, specify
Was Xpert run outside of a laboratory?	1 - Yes 0 - No
Current treatment: were patients on treatment (defined as tuberculosis drugs for longer than 7 days) for the current tuberculosis episode? (note: may impact culture results)	1 – Yes 2 – No 9 – Unknown/Not reported
If so, what is the percentage?	% Specify numerator/denominator
IV. Index test	
Xpert cartridge(s) evaluated	1 - Xpert only 2 - Ultra only 3 - Any combination Xpert and Ultra
Xpert platform: was Omni used? Unless Omni was 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
Pretreatment processing procedure for GeneXpert	1 – None 2 – NALC-NaOH 3 – NaOH (Petroff) 4 – Other 9 – Unknown/Not reported
For Xpert specimen, what was the condition of the specimen when tested?	1 – Fresh 2 – Frozen 9 – Unknown/Not reported
Were uninterpretable (invalid error or no result) results reported for Xpert for tuberculosis detection?	1 – Yes 9 – Unknown/Not reported If yes, describe numbers:
Were indeterminate results reported for Xpert for rifampicin resistance?	1 – Yes 9 – Unknown/Not reported If yes, describe numbers:
V. Reference standard	
For tuberculosis detection, what reference standard(s) was used?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a)

(Continued)

Respiratory samples?	3 – Both solid and liquid culture (specify 1a and 2a) 9 – Unknown/Not reported 1a - Solid culture LJ 7H10 7H11 Other 2a – Liquid culture MGIT 960 Other (specify):
For tuberculosis detection, what reference standard(s) was used? Lymph node?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 9 – Unknown/Not reported 1a - Solid culture LJ 7H10 7H11 Other 2a – Liquid culture MGIT 960 Other (specify):
For tuberculosis detection, what reference standard(s) was used? Cerebrospinal fluid?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 9 – Unknown/Not reported 1a - Solid culture LJ 7H10 7H11 Other (specify): 2a – Liquid culture MGIT 960 Other (specify):
Reference standard pulmonary tuberculosis: clinical	1 - Yes 0 – No Multiple answers, list:
If clinical, describe as in paper	
For rifampicin resistance detection, what reference standard(s) was used? Respiratory samples?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 4 – *M tuberculosis* DR*plus* 9 – Unknown/NR 1a - Solid culture LJ 7H10 7H11 Other: Specify method (e.g. proportion): 2a – Liquid culture MGIT 960 Other (specify):
For rifampicin resistance detection, what reference standard(s) was used?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a)

(Continued)

Lymph node?	3 – Both solid and liquid culture (specify 1a and 2a) 4 – *M tuberculosis* DR*plus* 9 – Unknown/Not reported 1a - Solid culture LJ 7H10 7H11 Other: Specify method (e.g. proportion): 2a – Liquid culture MGIT 960 Other (specify):
For rifampicin resistance detection, what reference standard(s) was used? Cerebrospinal fluid?	1 – Solid culture (specify 1a) 2 – Liquid culture (specify 2a) 3 – Both solid and liquid culture (specify 1a and 2a) 4 – *M tuberculosis* DR*plus* 9 – Unknown/Not reported 1a - Solid culture LJ 7H10 7H11 Other: Specify method (e.g. proportion): 2a – Liquid culture MGIT 960 Other (specify):
If information is available	
Is information on quality assurance of DST available in the study?	1 – Yes 2 - No 9 – Unknown/Not reported If yes, describe potential sources of bias

DST: drug susceptibility testing; IGRA: Interferon-gamma release assay; LJ: Löwenstein-Jensen; MDR-TB: multidrug-resistant tuberculosis; MGIT: mycobacterial growth indicator tube; NALC: N-acetyl-L-cysteine; NAOH: sodium hydroxide; TST: tuberculin skin test; WHO: World Health Organization.

Appendix 3. Example of 2 × 2 result table

Pulmonary tuberculosis, Xpert MTB/RIF		Tuberculosis, culture		
Xpert MTB/RIF in sputum		Yes	No	Total
	Positive			
	Negative			
	Total			

(Continued)

Pulmonary tuberculosis, Xpert Ultra		Tuberculosis, culture		
Xpert Ultra in sputum		Yes	No	Total
	Positive			
	Negative			
	Total			

Tuberculous meningitis		Tuberculosis, culture		
Xpert MTB/RIF in CSF		Yes	No	Total
	Positive			
	Negative			
	Total			

Pulmonary tuberculosis		Tuberculosis, CRS		
Xpert MTB/RIF in sputum		Yes	No	Total
	Positive			
	Negative			
	Total			

CRS: composite reference standard; CSF: cerebrospinal fluid.

Appendix 4. QUADAS-2 review-specific guidance

Domain 1 - Patient selection

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 if we could not tell.

Signalling question 2: did the study avoid inappropriate exclusions?

a. For pulmonary tuberculosis, we answered 'yes' for all studies because we did not think there were any inappropriate exclusions for children presumed to have pulmonary tuberculosis. For tuberculous meningitis and lymph node tuberculosis, we answered ‘no' if the study excluded specimens based on physical appearance (such as purulence) or a biochemical analysis (e.g. adenosine deaminase (ADA) or cell analysis). We answered ‘unclear' if we could not tell.

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

We are interested in how Xpert performs in patients who were evaluated as they would be in routine practice. Paediatric studies conducted in tertiary centres tend to include a larger number of children with advanced disease; therefore we answered ‘low concern' if patients

were evaluated in local hospitals or primary care centres; 'high concern' if patients were evaluated exclusively as inpatients in tertiary care centres; and 'unclear concern' if the clinical setting was not reported or if information was insufficient to justify a decision. We also answered 'unclear concern' if Xpert testing was done at a reference laboratory and the clinical setting was not reported because it is difficult to tell if a given reference laboratory provides services mainly to very sick patients (inpatients in tertiary care) or to patients with a broad spectrum of disease, including very sick patients and those with less severe disease (primary, secondary, and tertiary care).

Domain 2 - Index test

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 results of the reference standard? We answered this question 'yes' for all studies because Xpert MTB/RIF and Xpert Ultra test results are automatically generated, and the user is 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 pre-specified? The threshold is pre-specified in all versions of Xpert MTB/RIF and Xpert Ultra. We answered this question 'yes' for all studies.

Applicability: are there concerns that the index test, its conduct, or its interpretation differs from the review question? Variations in test technology, execution, or interpretation may affect estimates of the diagnostic accuracy of a test. GeneXpert, the test device platform, simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification, and detection) required for real-time polymerase chain reaction (PCR)-based molecular testing. All steps in the Xpert MTB/RIF and Xpert Ultra assays are completely automated and self-contained following sample loading. Minimal training is required for operators such as laboratory technicians and nurses to run the index test.

For pulmonary tuberculosis, we answered 'low concern' if the index test was performed as recommended by the manufacturer. For sputum specimens, we answered 'unclear concern' if the ratio of the Xpert sample reagent: specimen volume was not 2:1 for a raw specimen or 3:1 for a centrifuged sediment, as recommended by the manufacturer, or if we could not tell (WHO 2014a). Central-level laboratories use more highly trained staff than peripheral- and intermediate-level laboratories or health facilities. However, we do not consider this to be a concern about applicability due to the minimal training required to run the index tests.

With respect to extrapulmonary specimens, the WHO has provided detailed information about processing steps in the 'Xpert MTB/RIF implementation manual'. Technical and operational "how-to" practical considerations. Annex 2 - Standard operating procedure (SOP) for processing extrapulmonary specimens (CSF, lymph nodes, and other tissues) for "Xpert MTB/RIF assay"' (WHO 2014b). For extrapulmonary specimens, we answered 'low concern' if the test was performed according to WHO standard operating procedures. We answered 'high concern' if the test was performed in a way that deviated from these recommendations. We answered 'unclear concern' if we could not tell.

Domain 3 - Reference standard

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

Signalling question 1.a: is a culture reference standard likely to correctly classify the target condition?
For pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis, we anticipated that the vast majority of studies would perform culture. Culture is generally considered the best reference standard for tuberculosis diagnosis. However, particularly in children with paucibacillary disease, tuberculosis is verified by culture in only 15% to 50% of cases, depending on disease severity, challenges of obtaining specimens, and resources (Graham 2015). Evaluation of multiple specimens may increase the yield of culture for confirming tuberculosis (Cruz 2012; Zar 2012). We answered 'yes' for studies using multiple specimens and 'unclear' for studies using only one specimen.

Signalling question 1.b: is the composite reference standard likely to correctly classify the target condition? A composite reference standard aims to classify children who were not detected by culture. The definition of the composite reference standard is heterogeneous across studies. Irrespective of how tuberculosis was defined in the publications, we classified children as having tuberculosis if they were presumed to have tuberculosis and were started on anti-tuberculosis treatment. For a composite reference standard, we answered 'unclear' for all studies.

For rifampicin resistance, we answered 'yes' if a study used phenotypic culture-based drug susceptibility testing or MTBDR*plus* as the reference standard. As this is an inclusion criterion for the review, we answered 'yes' for all studies.

Signalling question 2: were the reference standard results interpreted without knowledge of results of the index test? For pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis, we answered 'yes' if the reference test provided an automated result (e.g. MGIT 960); blinding was explicitly stated; or it was clear that the reference standard was performed at a separate laboratory or performed by different people. We answered 'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert test result. We answered 'unclear' if we could not tell.
For rifampicin resistance, we answered 'yes' if the reference test provided an automated result (e.g. MGIT 960 SIRE); blinding was explicitly stated; or it was clear that the reference standard was performed at a separate laboratory or performed by different people. We answered

'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert 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?

For pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis, we answered 'high concern' if the included studies did not differentiate *Mycobacterium tuberculosis* complex isolated in culture from other mycobacteria using any speciation technique; 'low concern' if speciation was performed using any technique; and 'unclear concern' if we could not tell.

For rifampicin resistance, we considered applicability to be of 'low concern' for all studies because the method used (phenotypic culture-based drug susceptibility testing or MTBDR*plus*) is appropriate.

Domain 4 - Flow and timing

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

Signalling question 1: was there an appropriate interval between the index test and the reference standard? We expected to find for most included studies that specimens for Xpert and culture were obtained at the same time when patients were evaluated for presumed tuberculosis. Even if there were a delay of several days between index test and reference standards, tuberculosis is a chronic disease, and we consider 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 the reference standard were performed at the same time, or if the time interval was less than or equal to seven days; 'no' if the time interval was greater than seven days; and 'unclear' if we could not tell.

Signalling question 2: did all patients receive the same reference standard? We answered 'yes' if all patients received the same reference standard; 'no' if all patients did not receive the same reference standard; and 'unclear' if we could not tell.

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 × 2 tables. We answered 'yes' if the numbers matched, and 'no' if there were patients enrolled in the study who were not included in the analysis. We answered 'unclear' if we could not tell.

Judgements for risk of bias assessments for a given domain.

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

HISTORY

Protocol first published: Issue 6, 2019
Review first published: Issue 8, 2020

CONTRIBUTIONS OF AUTHORS

AK, LFG, KRS, and AMM assessed articles for inclusion and extracted data.

AK and KRS entered data in RevMan.

AK, YT, KRS, and AMM analysed the data and interpreted the analyses. In particular, YT performed statistical analyses.

AK, LFG, YT, KRS, and AMM drafted the manuscript.

ME and AD provided critical comments on the manuscript.

All review authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

AK has conducted prior primary research on tuberculosis diagnostics. The Baylor College of Medicine Children's Foundation-Swaziland, where Dr. Kay is based, received a discount from Cepheid on Xpert MTB/RIF Ultra cartridges for a tuberculosis case finding programme. The Baylor College of Medicine Children's Foundation-Swaziland is separate from Baylor College of Medicine (AK's employer).

LGF has no known conflicts of interest.

YT has no known conflicts of interest.

ME has no known conflicts of interest.

AD has conducted prior primary research on tuberculosis diagnostics and has no known conflicts of interest.

KRS has received financial support for the preparation of systematic reviews and educational materials, consultancy fees from FIND (for the preparation of systematic reviews), honoraria, and travel support to attend WHO guidelines meetings.

AMM has conducted prior primary research on tuberculosis diagnostics and has no known conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We defined the microbiological reference standard as culture only and did not include smear microscopy, which is less accurate. For stool, we accepted as a reference standard a positive result by Xpert MTB/RIF or Xpert Ultra in a sputum specimen. For the composite reference standard, when information about tuberculosis treatment was not available, we accepted the uniform research definition (Graham 2012; Graham 2015). In these situations, using the older definition (Graham 2012), we defined tuberculosis as (1) confirmed, probable, and possible cases, and (2) non-tuberculosis. For the newer definition (Graham 2015), we used the categories tuberculosis confirmed and not confirmed. In cases where a study-specific definition for the composite references standard was applied, this was accepted as well. For studies in which gastric aspirate specimens and sputum specimens were collected, data were included with the sputum analyses, and we performed a sensitivity analysis excluding these studies. We added MTBDR*plus,* a WHO-recommended test, as a reference standard for rifampicin resistance. We had planned to estimate the pooled proportion of uninterpretable Xpert MTB/RIF and Xpert Ultra results for tuberculosis detection and indeterminate Xpert MTB/RIF and Xpert Ultra results for rifampicin resistance detection. However, we found few uninterpretable results reported. We have summarized these results in a table with the key characteristics of the included studies. We did not perform an indirect test comparison of Xpert MTB/RIF and Xpert Ultra because there were only three Ultra studies. These three studies also assessed Xpert MTB/RIF, and so we limited our analysis to a direct comparison. Owing to limited data, we were able to perform investigations of heterogeneity and sensitivity analyses only for Xpert MTB/RIF. Finally, as part of the analysis for the World Health Organization Molecular Diagnostics Guideline Development Group, we were asked to provide data on the diagnostic accuracy of multiple Xpert tests compared with a single Xpert test in children; this analysis has been added to the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotics, Antitubercular [therapeutic use]; Bias; Feces [microbiology]; Gastrointestinal Contents [microbiology]; Molecular Typing [*methods] [standards]; Mycobacterium tuberculosis [drug effects] [isolation & purification]; Rifampin [therapeutic use]; Sensitivity and Specificity; Sputum [microbiology]; Tuberculosis, Lymph Node [*diagnosis] [drug therapy] [microbiology]; Tuberculosis, Meningeal [cerebrospinal fluid] [*diagnosis] [drug therapy] [microbiology]; Tuberculosis, Multidrug-Resistant [*diagnosis] [drug therapy] [microbiology]; Tuberculosis, Pulmonary [*diagnosis] [drug therapy] [microbiology]

MeSH check words

Adolescent; Child; Humans