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[Diagnostic Test Accuracy Review]

Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children

Alexander W Kay^{1a}, Maia Madison², Katie Scandrett³, Tara Ness⁴, Pauline Amuge⁵, Leeberk Raja Inbaraj⁶, Mukesh Kumar Sathya Narayanan⁷, Lucia González Fernández⁴, Michael Eisenhut⁸, Nazir Ismail⁹, Alexei Korobitsyn⁹, Sabine E Verkuijl⁹, Annemieke Brands⁹, Kerri Viney⁹, Tiziana Masini⁹, Anna M Mandalakas¹, Karen R Steingart¹⁰, Yemisi Takwoingi³

¹The Global Tuberculosis Program, Texas Children's Hospital, Section of Global Health, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA. ²Global TB Program, Baylor College of Medicine, Mbabane, Eswatini. ³Department of Applied Health Sciences, University of Birmingham, Birmingham, UK. ⁴The Global Tuberculosis Program, Texas Children's Hospital, Section of Global and Immigrant Health, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA. ⁵Joint Clinical Research Center, Research Directorate, Lubowa, Uganda. ⁶ICMR - National Institute for Research in Tuberculosis, Chennai, India. ⁷Epidemiology, ICMR - National Institute for Research in Tuberculosis, Chennai, India. ⁸Paediatric Department, Luton & Dunstable University Hospital NHS Foundation Trust, Luton, UK. ⁹Global Programme on Tuberculosis and Lung Health, World Health Organization, Geneva, Switzerland. ¹⁰Honorary Research Fellow (retired), Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

^aORCID iD: <https://orcid.org/0000-0001-5283-4697>

Contact: Alexander W Kay, alexander.kay@bcm.edu.

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ABSTRACT

Background

In 2023, an estimated 1.3 million children (aged 0–14 years) became ill with tuberculosis, and 166,000 children (aged 0–15 years) died from the disease. Xpert MTB/RIF Ultra (Xpert Ultra) is a molecular World Health Organization (WHO)-recommended rapid diagnostic test that detects *Mycobacterium tuberculosis* complex and rifampicin resistance. This is an update of a Cochrane review first published in 2020 and last updated in 2022. Parts of the current update informed the 2024 WHO updated guidance for the diagnosis of tuberculosis.

Objectives

To assess the diagnostic accuracy of Xpert Ultra for detecting pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance in children (aged 0–9 years) with presumed tuberculosis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, three other databases, and three trial registers without language restrictions to 6 October 2023.

Selection criteria

For study design, we included cross-sectional and cohort studies and randomized trials that evaluated Xpert Ultra in HIV-positive and HIV-negative children aged birth to nine years. Regarding specimen type, we included studies evaluating sputum, gastric, stool, or

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nasopharyngeal specimens (pulmonary tuberculosis); cerebrospinal fluid (tuberculous meningitis); and fine needle aspirate or surgical biopsy tissue (lymph node tuberculosis). Reference standards for detection of tuberculosis were microbiological reference standard (MRS; including culture) or composite reference standard (CRS); for stool, we considered Xpert Ultra in sputum or gastric aspirates in addition to culture. Reference standards for detection of rifampicin resistance in sputum were phenotypic drug susceptibility testing or targeted or whole genome sequencing.

Data collection and analysis

Two review authors independently extracted data and assessed methodological quality using the tailored QUADAS-2 tool, judging risk of bias separately for each target condition and sample type. We conducted separate meta-analyses for detection of pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance. We used a bivariate model to estimate summary sensitivity and specificity with 95% confidence intervals (CIs). We assessed certainty of evidence using the GRADE approach.

Main results

This update included 23 studies (including 9 new studies since the previous review) that evaluated detection of pulmonary tuberculosis (21 studies, 9223 children), tuberculous meningitis (3 studies, 215 children), lymph node tuberculosis (2 studies, 58 children), and rifampicin resistance (3 studies, 130 children). Seventeen studies (74%) took place in countries with a high tuberculosis burden. Overall, risk of bias and applicability concerns were low.

Detection of pulmonary tuberculosis (microbiological reference standard)

Sputum (11 studies)

Xpert Ultra summary sensitivity was 75.3% (95% CI 68.9% to 80.8%; 345 children; moderate-certainty evidence), and specificity was 95.9% (95% CI 92.3% to 97.9%; 2645 children; high-certainty evidence).

Gastric aspirate (12 studies)

Xpert Ultra summary sensitivity was 69.6% (95% CI 60.3% to 77.6%; 167 children; moderate-certainty evidence), and specificity was 91.0% (95% CI 82.5% to 95.6%; 1792 children; moderate-certainty evidence).

Stool (10 studies)

Xpert Ultra summary sensitivity was 68.0% (95% CI 50.3% to 81.7%; 255 children; moderate-certainty evidence), and specificity was 98.2% (95% CI 96.3% to 99.1%; 2630 children; high-certainty evidence).

Nasopharyngeal aspirate (6 studies)

Xpert Ultra summary sensitivity was 46.2% (95% CI 34.9% to 57.9%; 94 children; moderate-certainty evidence), and specificity was 97.5% (95% CI 95.1% to 98.7%; 1259 children; high-certainty evidence).

Xpert Ultra sensitivity was lower against CRS than against MRS for all specimen types, while the specificities were similar.

Extrapulmonary tuberculosis

Meta-analysis was not possible for lymph node tuberculosis and tuberculous meningitis due to low study numbers.

Interpretation of results

For a population of 1000 children, where 100 have pulmonary tuberculosis:

In sputum:

- 112 would be Xpert Ultra positive, of whom 75 would have pulmonary tuberculosis (true positives) and 37 would not (false positives).
- 888 would be Xpert Ultra negative, of whom 863 would not have pulmonary tuberculosis (true negatives) and 25 would have pulmonary tuberculosis (false negatives).

In gastric aspirate:

- 151 would be Xpert Ultra positive, of whom 70 would have pulmonary tuberculosis (true positives) and 81 would not (false positives).
- 849 would be Xpert Ultra negative, of whom 819 would not have pulmonary tuberculosis (true negatives) and 30 would have pulmonary tuberculosis (false negatives).

In stool:

- 85 would be Xpert Ultra positive, of whom 68 would have pulmonary tuberculosis (true positives) and 17 would not (false positives).
- 915 would be Xpert Ultra negative, of whom 883 would not have pulmonary tuberculosis (true negatives) and 32 would have pulmonary tuberculosis (false negatives).

In nasopharyngeal aspirate:

- 68 would be Xpert Ultra positive, of whom 46 would have pulmonary tuberculosis (true positives) and 22 would not (false positives).
- 932 would be Xpert Ultra negative, of whom 878 would not have pulmonary tuberculosis (true negatives), and 54 would have pulmonary tuberculosis (false negatives).

Detection of rifampicin resistance

Three studies with 76 children evaluated detection of rifampicin resistance (sputum only); two of these studies reported no cases and one reported rifampicin resistance in two children.

Authors' conclusions

Xpert Ultra sensitivity was moderate in sputum, gastric aspirate, and stool specimens. Nasopharyngeal aspirate had the lowest sensitivity. Xpert Ultra specificity was high against both MRS and CRS. We were unable to determine the accuracy of Xpert Ultra for detecting tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance due to a paucity of data.

Funding

This update was funded through WHO.

Registration

The protocol for this review was originally published through Cochrane in 2019. The protocol for this update was a generic protocol that consolidated previously published Cochrane protocols of Xpert Ultra for tuberculosis detection and can be accessed at <https://osf.io/26wg7/>.

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Original review (2020) DOI: 10.1002/14651858.CD013359.pub2

Review update (2022) DOI: 10.1002/14651858.CD013359.pub3

PLAIN LANGUAGE SUMMARY

What is the accuracy of Xpert Ultra for diagnosing tuberculosis and resistance to rifampicin (an antibiotic) in children?

Key Messages

- Xpert Ultra in samples of sputum (mucus coughed up from the lungs), gastric aspirate (mucus and saliva suctioned from the stomach), and stool (faeces) is accurate for detecting pulmonary tuberculosis in children.
- The risk of missing a diagnosis of pulmonary tuberculosis is present, but the risk of incorrectly diagnosing a child as having pulmonary tuberculosis is low.

Why is improving the diagnosis of tuberculosis important?

In 2023, an estimated 1.3 million children became ill with tuberculosis, a disease caused by the bacteria *Mycobacterium tuberculosis*. Not recognizing tuberculosis (false negative results) may result in delayed diagnosis, severe illness, and death. An incorrect tuberculosis diagnosis (false positive results) may result in unnecessary treatment.

What was the aim of this review?

To assess the accuracy of Xpert Ultra for diagnosing tuberculosis affecting the lungs (pulmonary tuberculosis), central nervous system and brain (tuberculous meningitis), and lymph nodes, and for detecting resistance to rifampicin (an antibiotic used to treat tuberculosis), in children aged under 10 years who have symptoms of tuberculosis.

What did this review study?

Xpert Ultra simultaneously detects *Mycobacterium tuberculosis* and resistance to rifampicin. For *Mycobacterium tuberculosis* detection, we assessed results against two benchmarks: culture (a method used to grow the germ) and a composite disease definition based on symptoms, chest X-ray, and culture. For rifampicin resistance detection, we assessed results against drug susceptibility testing or genome sequencing (methods for identifying drug resistance mutations).

What were the main results of this review?

We included 23 studies in total. Most studies looked at pulmonary tuberculosis (21 studies, 9223 children). Three studies investigated rifampicin resistance, three investigated tuberculous meningitis, and two investigated lymph node tuberculosis.

For a population of 1000 children where 100 have pulmonary tuberculosis (according to culture results):

In sputum:

- 112 would be Xpert Ultra positive, of whom 75 would have pulmonary tuberculosis (true positives) and 37 would not (false positives).
- 888 would be Xpert Ultra negative, of whom 863 would not have pulmonary tuberculosis (true negatives) and 25 would have pulmonary tuberculosis (false negatives).

In gastric aspirate:

- 151 would be Xpert Ultra positive, of whom 70 would have pulmonary tuberculosis (true positives) and 81 would not (false positives).
- 849 would be Xpert Ultra negative, of whom 819 would not have pulmonary tuberculosis (true negatives) and 30 would have pulmonary tuberculosis (false negatives).

In stool:

- 85 would be Xpert Ultra positive, of whom 68 would have pulmonary tuberculosis (true positives) and 17 would not (false positives).
- 915 would be Xpert Ultra negative, of whom 883 would not have pulmonary tuberculosis (true negatives) and 32 would have pulmonary tuberculosis (false negatives).

In nasopharyngeal aspirate:

- 68 would be Xpert Ultra positive, of whom 46 would have pulmonary tuberculosis (true positives) and 22 would not (false positives).
- 932 would be Xpert Ultra negative, of whom 878 would not have pulmonary tuberculosis (true negatives) and 54 would have pulmonary tuberculosis (false negatives).

In the three studies that looked at rifampicin resistance (in 76 children), only two children had rifampicin resistance.

The percentage of children with tuberculous meningitis detected by Xpert Ultra ranged between 67% and 100% (215 children in total, 13 with culture-confirmed tuberculous meningitis) in three studies. Xpert Ultra confirmed 100% of children with culture-confirmed lymph node tuberculosis in two studies (58 children in total, 21 with culture-confirmed lymph node tuberculosis).

What are the limitations of the evidence?

For pulmonary tuberculosis, we are moderately confident in our results. We included studies from different countries and used two different reference standards, although neither reference standard is perfect. We are less confident in the results for rifampicin resistance, because only three studies investigated this aspect, and only three children showed resistance to rifampicin. We could not combine results on lymph node tuberculosis or tuberculous meningitis from different studies because few studies investigated these types of tuberculosis.

Who do the results of this review apply to?

The review applies to children (birth–9 years) who are living with HIV or are HIV negative, with signs or symptoms of pulmonary tuberculosis, tuberculous meningitis, or lymph node tuberculosis. The results also apply to children with severe malnutrition and tuberculosis symptoms. The results apply mainly to children living in parts of the world with high rates of tuberculosis or tuberculosis and HIV.

What are the implications of this review?

The results suggest that in children aged under 10 years, Xpert Ultra is moderately accurate for detecting pulmonary tuberculosis in samples of sputum, gastric aspirate, and stool. The accuracy in nasopharyngeal aspirate samples is lower.

When using Xpert Ultra, the risk of not diagnosing pulmonary tuberculosis (confirmed by culture) is still present, suggesting that clinicians should not rely on Xpert Ultra alone.

How up to date is this review?

This review updates our previous review and includes evidence published up to 6 October 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Xpert Ultra for detection of pulmonary tuberculosis in children^a

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

Patients/population: children with presumed pulmonary tuberculosis

Index tests: Xpert Ultra

Role: an initial test

Threshold for index tests: an automated result is provided.

Reference standard: culture (for stool, Ultra performed on a respiratory specimen was included in the microbiological reference standard)

Types of studies: cross-sectional and cohort studies

Setting: primary care facilities and local hospitals

| Specimen | Effect (95% CI) | Number of children (studies) | Test result | Number of results per 1000 patients tested(95% CI) ^b | | | Certainty of the evidence (GRADE) |
|------------------|--|------------------------------|----------------|---|------------------|------------------|-------------------------------------|
| | | | | Prevalence 1% | Prevalence 5% | Prevalence 10% | |
| Sputum | Summary sensitivity 75.3% (68.9% to 80.8%) | 345 (11) | True positive | 8 (7 to 8) | 41 (21 to 76) | 75 (69 to 81) | ⊕⊕⊕⊕ Moderate^c |
| | | | False negative | 2 (2 to 3) | 12 (10 to 16) | 25 (19 to 31) | |
| | Summary specificity 95.9% (92.3% to 97.9%) | 2645 (11) | True negative | 949 (914 to 969) | 12 (10 to 16) | 863 (831 to 881) | ⊕⊕⊕⊕ High |
| | | | False positive | 41 (21 to 76) | 39 (20 to 73) | 37 (19 to 69) | |
| | Summary sensitivity 69.6% (60.3% to 77.6%) | 167 (12) | True positive | 7 (6 to 8) | 35 (30 to 39) | 70 (60 to 78) | ⊕⊕⊕⊕ Moderate^d |
| | | | False negative | 3 (2 to 4) | 15 (11 to 20) | 30 (22 to 40) | |
| Gastric aspirate | Summary specificity 91.0% (82.5% to 95.6%) | 1792 (12) | True negative | 901 (817 to 946) | 864 (784 to 908) | 819 (742 to 860) | ⊕⊕⊕⊕ |

| | | | | | | | |
|------------------------------|---|--------------|----------------|------------------|------------------|------------------|-----------------------------|
| | | | False positive | 89 (44 to 173) | 86 (42 to 166) | 81 (40 to 158) | Moderate^e |
| Stool | Summary sensitivity 68.0% (50.3% to 81.7%) | 255 (10) | True positive | 7 (5 to 8) | 34 (25 to 39) | 68 (50 to 82) | ⊕⊕⊕⊕ |
| | | | False negative | 3 (2 to 5) | 16 (9 to 25) | 32 (18 to 50) | Moderate^f |
| | Summary specificity 98.2% (96.3% to 99.1%) | 2630 (10) | True negative | 971 (953 to 981) | 932 (915 to 941) | 883 (867 to 892) | ⊕⊕⊕⊕ |
| | | | False positive | 19 (9 to 37) | 18 (9 to 35) | 17 (8 to 33) | High |
| Nasopharyn- geal aspirate | Summary sensitivity 46.2% (34.9% to 57.9%) | 94 (6) | True positive | 5 (3 to 6) | 23 (17 to 29) | 46 (35 to 58) | ⊕⊕⊕⊕ |
| | | | False negative | 5 (4 to 7) | 27 (21 to 33) | 54 (42 to 65) | Moderate^g |
| | Summary specificity 97.5% (95.1% to 98.7%) | 1259 (6) | True negative | 965 (941 to 977) | 926 (903 to 938) | 878 (856 to 888) | ⊕⊕⊕⊕ |
| | | | False positive | 25 (13 to 49) | 24 (12 to 47) | 22 (12 to 44) | High |

GRADE Working Group grades of evidence

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

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

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

CI: confidence interval.

^a 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.

^b Prevalence levels were suggested by the World Health Organization (WHO) Global Tuberculosis Programme.

^c Downgraded one level for inconsistency as sensitivity ranges from 57% to 91%.

^d Downgraded one level for inconsistency as sensitivity ranges from 0% to 100%.

^e Downgraded one level for inconsistency as specificities range from 68% to 100%, and some CIs do not overlap.

^f Downgraded one level for inconsistency as sensitivities range from 26% to 100%, and some CIs do not overlap.

^g Downgraded one level due to the small number of children included in the analysis (n = 94).

Summary of findings 2. Xpert Ultra for detection of rifampicin resistance in children^a

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

Patients/population: children with presumed pulmonary tuberculosis

Index tests: Xpert Ultra

Role: an initial test

Threshold for index tests: an automated result is provided.

Reference standard: culture-based phenotypic drug susceptibility testing and targeted or whole genome sequencing on sputum

Types of studies: cross-sectional and cohort studies

Setting: primary care facilities and local hospitals

Limitations: the findings are based on three studies and two children with rifampicin resistance.

| Specimen | Effect (95% CI) | Number of children (studies) | Test result | Number of results per 1000 patients tested(95% CI) ^b | | | Certainty of the evidence (GRADE) |
|---------------|--------------------------------|------------------------------|----------------|---|----------------|----------------|-----------------------------------|
| | | | | Prevalence 2% | Prevalence 10% | Prevalence 15% | |
| All specimens | Sensitivity range 100% to 100% | 2 (3) | True positive | 20 to 20 | 100 to 100 | 150 to 150 | ⊕⊕⊕⊕ |
| | | | False negative | 0 to 0 | 0 to 0 | 0 to 0 | Very low ^{c,d} |
| | Specificity range 100% to 100% | 76 (3) | True negative | 951 to 980 | 873 to 900 | 825 to 850 | ⊕⊕⊕⊕ |
| | | | False positive | 0 to 29 | 0 to 27 | 0 to 25 | Moderate ^d |

GRADE Working Group grades of evidence

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

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

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

Abbreviations: CI: confidence interval.

^a The results presented in this table should not be interpreted in isolation from the results of individual included studies contributing to sensitivity and specificity.

^b Prevalence levels were suggested by the WHO Global Tuberculosis Programme.

^c Downgraded two levels for imprecision because only two children with rifampicin resistance contributed to this analysis for the observed sensitivity.

^d Downgraded one level for risk of bias because in one study, the manner of participant selection was unclear, and in another, not all children were included in the analysis.

BACKGROUND

Tuberculosis is one of the top 10 causes of death and a leading cause from a single infectious agent. In 2023, an estimated 10.8 million people developed tuberculosis disease worldwide, including around 1.3 million children younger than 15 years. That same year, an estimated 1.25 million people died of the disease, including 166,000 children [1]. Recent complementary models of the global mortality burden that have been accepted and supported by the World Health Organization (WHO) indicate substantial under-reporting and underdiagnosis of tuberculosis in children. Furthermore, a higher proportion of children than adults die out of total estimated tuberculosis cases [2, 3]. Estimates suggest that most deaths among children occur in undiagnosed episodes and represent a missed opportunity to start treatment [3].

In 2019, in preparation for a WHO Guideline Development Group Meeting to update recommendations on the use of rapid molecular assays intended as initial tests for diagnosing pulmonary and extrapulmonary tuberculosis, we performed a Cochrane review to assess the diagnostic accuracy of Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) for tuberculosis disease and rifampicin resistance in children [4]. In 2022, the review was updated for the Guideline Development Group Meeting on the management of tuberculosis in children and adolescents using a microbiological reference standard (MRS, culture), or a composite reference standard (CRS) [5].

In December 2020, WHO introduced a class-based recommendation approach and three new classes of nucleic acid amplification tests (NAATs): low-complexity automated NAATs (LC-aNAATs), low-complexity manual NAATs (LC-mNAATs), and moderate-complexity automated NAATs (MC-aNAATs). The classes are defined by the type of technology, the complexity of implementing the test (e.g. low, moderate, or high, considering the requirements of infrastructure, equipment, and technical skills of laboratory staff) and the target conditions (e.g. diagnosis of tuberculosis and detection of resistance to first-line or second-line drugs) [6]. Xpert Ultra is an LC-aNAAT.

In preparation for the 2024 Guideline Development Group Meeting on tuberculosis diagnosis, we updated our 2022 review. This updated review focuses on the diagnostic accuracy of Xpert Ultra in sputum, gastric aspirate, nasopharyngeal aspirate, and stool specimens for the diagnosis of pulmonary tuberculosis and rifampicin resistance in children. Based on the WHO definition of a child according to age group, we included only children younger than 10 years in this review update. We also included data on the performance of Xpert Ultra for the diagnosis of tuberculous meningitis and lymph node tuberculosis.

Target condition being diagnosed

Our target conditions are pulmonary tuberculosis, extrapulmonary tuberculosis (including two subcategories: tuberculous meningitis and lymph node tuberculosis), and rifampicin resistance.

Tuberculosis

Tuberculosis is an infectious disease caused by bacteria from the *Mycobacterium tuberculosis* complex, most commonly *M tuberculosis*. Typically spread 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. For this review, we limited evaluation of extrapulmonary tuberculosis to tuberculous meningitis and lymph node tuberculosis. Tuberculous meningitis results in the highest morbidity and mortality [7], and lymph node tuberculosis is the most common form of extrapulmonary tuberculosis in children [8].

The natural history of tuberculosis in children is distinct from that in adults, due to more frequent progression to primary tuberculosis disease [9]. Children younger than five years of age are at particularly high risk of progression to tuberculosis disease following infection, but the risk for older children and adolescents is also higher than in adults. Overall, it is estimated that 90% of tuberculosis disease in young children occurs within one year of infection [10]. In addition to age, factors such as nutritional status, immune-compromising conditions (e.g. HIV infection), bacillus Calmette-Guérin (BCG) vaccination status, and genetic susceptibility contribute to children's risk of disease progression. Immediately following infection with *M tuberculosis* in a child, haematogenous 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 tuberculosis 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 tuberculous meningitis and miliary tuberculosis [9, 10]. Children younger than five years of age 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 or cavitations [9].

Laboratory confirmation of tuberculosis in children is challenging for two reasons. First, tuberculosis in children most commonly presents as a primary disease process, without the formation of cavities [11]. The number of bacilli (the presence of bacilli on a specimen usually 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, tuberculosis in children is often referred to as 'paucibacillary', and it is more difficult to obtain the bacilli needed to confirm disease via conventional smear (no longer recommended) or culture [12]. 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. Because children swallow respiratory secretions, early-morning gastric aspiration is another well-established (yet still invasive) 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 [13]. Nasopharyngeal aspiration for respiratory specimens is a less invasive mode of specimen collection that can be performed in decentralized clinical environments [14]. Stool is also a WHO-recommended tuberculosis diagnostic specimen in children; this option is highly practical because collection is non-invasive and requires no training [15]. 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 tuberculosis in this population. However,

these algorithms have been shown to perform differently across settings, and their sensitivity and specificity may be site-specific [16]. WHO recently published two treatment decision algorithms as part of the WHO operational handbook on tuberculosis (Module 5: Management of tuberculosis in children and adolescents), and is seeking additional evidence on the accuracy of the treatment decision algorithms in multiple settings.

Rifampicin-resistant tuberculosis

Rifampicin-resistant tuberculosis is caused by *M tuberculosis* strains resistant to rifampicin, a critical first-line tuberculosis drug (see [Index test\(s\)](#)). These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant (MDR) tuberculosis) or resistant to other first-line or second-line tuberculosis drugs [17]. People with drug-resistant tuberculosis can transmit the drug-resistant strain to others. WHO has issued recommendations that all individuals with MDR or rifampicin-resistant tuberculosis, including those who are also resistant to fluoroquinolones, may benefit from all-oral treatment regimens [17].

Index test(s)

The index test is Xpert Ultra (Cepheid Inc, Sunnyvale, CA, USA). Xpert Ultra is an LC-aNAAT that functions as an automated closed system for performing 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 test detects both live and dead *M tuberculosis* complex DNA and simultaneously recognizes mutations in the *M tuberculosis* gene encoding the beta subunit of the ribonucleic acid (RNA) polymerase (*rpoB*) gene, which is the most common site of *M tuberculosis* mutations leading to rifampicin resistance. Xpert Ultra uses the same platform (GeneXpert) as Xpert MTB/RIF. Xpert Ultra requires an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules. WHO has published extensive guidance and practical information on implementing the test [6].

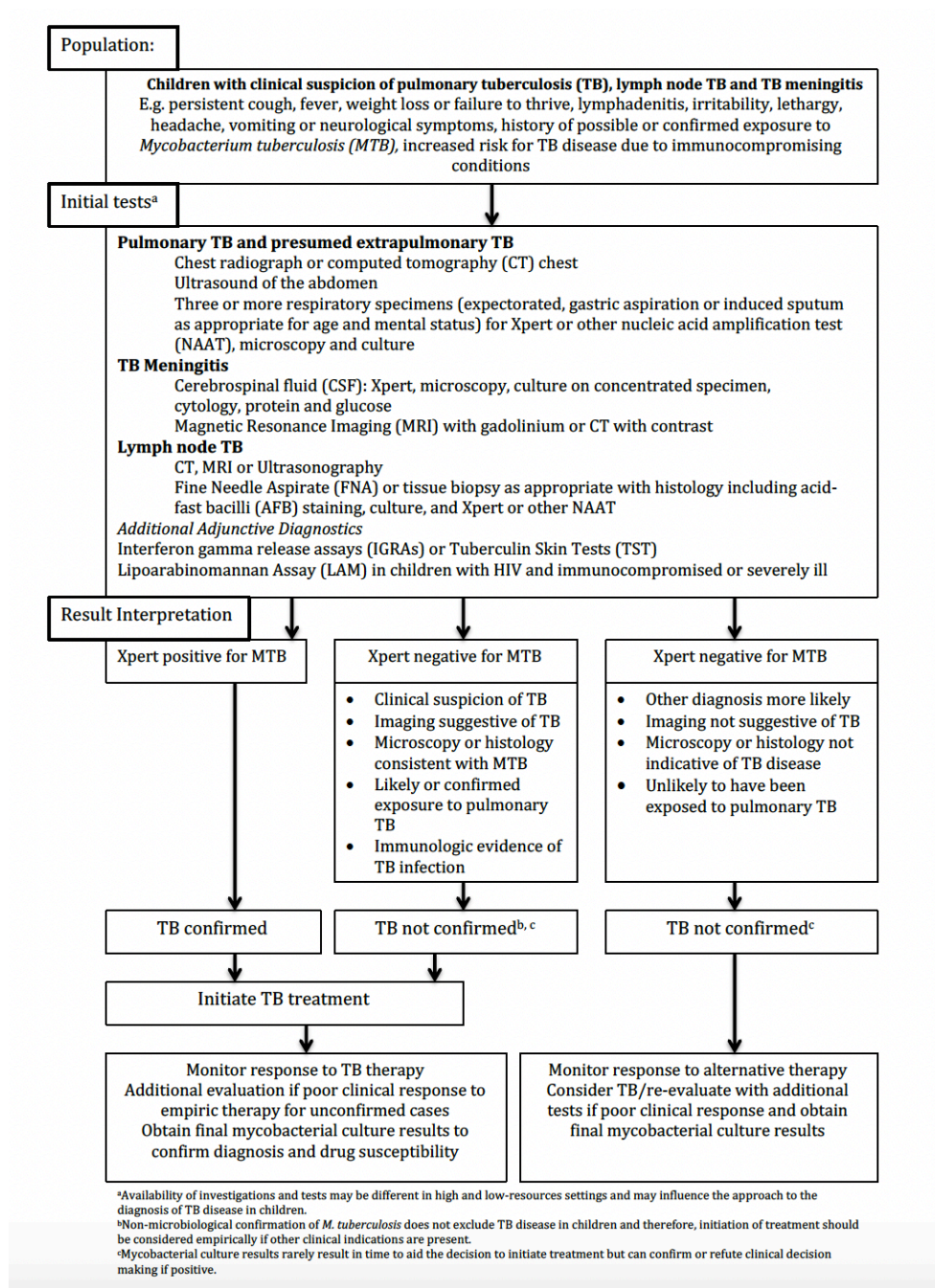
Xpert Ultra was designed to improve the sensitivity of detecting *M tuberculosis* complex and the reliability of detecting rifampicin

resistance [6]. To improve tuberculosis detection, Xpert Ultra incorporates two different multicopy amplification targets (IS6110 and IS1081) and a larger chamber for the PCR reaction. To improve rifampicin resistance detection, Xpert Ultra is based on melting temperature analysis. At very low bacterial loads, Xpert Ultra can give a trace result (considered a positive bacteriologic result in children and people with HIV), though trace does not provide a result for rifampicin susceptibility or resistance. Studies have found that the increase in Xpert Ultra sensitivity for tuberculosis detection has been accompanied by a decrease in specificity, and that Xpert Ultra may be more likely to identify *M tuberculosis* DNA from prior episodes of tuberculosis, particularly in people with a trace result [18, 19]. Despite clear guidance in children, Xpert Ultra trace results can complicate decision making, and clinical management of trace results is rarely straightforward.

Clinical pathway

Figure 1 presents an example of the clinical pathway and placement of the index test. A careful clinical history of tuberculosis exposure and symptoms is the first step in the diagnostic pathway for tuberculosis in children. Children with household or other close and persistent exposure to a person with tuberculosis are at increased risk of tuberculosis infection and subsequent progression to tuberculosis disease. All children with recent exposure to tuberculosis must be evaluated for clinical symptoms consistent with tuberculosis disease. Additional testing depends on the context but may include chest radiography and a test of tuberculosis infection. Symptoms of tuberculosis disease generally persist for longer than two weeks and are unremitting [20]. 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 shown to be reliable in multiple contexts. Symptom-based diagnostic algorithms tend to perform poorly in children younger than three years of age and in HIV-positive children – two populations at high risk for disease progression [21].

Figure 1. Clinical pathway of Xpert Ultra in children presumed to have tuberculosis.



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 tuberculosis disease and should modify diagnostic algorithms accordingly. HIV infection not only significantly increases the risk of tuberculosis in children; 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 for tuberculosis infection, such as interferon gamma release assays or tuberculin skin tests, can also aid in establishing the probability of tuberculosis disease 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 or nasopharyngeal aspirates are increasingly used. To diagnose extrapulmonary tuberculosis, sample collection targets the affected site of disease.

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

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

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

- False positive: children (and their families) likely experience anxiety and morbidity caused by additional testing, unnecessary treatment, and possible adverse effects. Other negative consequences include missed time from 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, as well as the risk of missing an important alternative diagnosis.
- False negative: this implies an increased risk of morbidity and mortality and delayed start of treatment.

Prior test(s)

Prior tests may include clinical history taking, physical examination, and imaging.

Role of index test(s)

For tuberculosis detection, the index test would be used as an initial test, replacing standard practice (i.e. smear microscopy or culture). For detection of rifampicin resistance, the index test would replace culture-based drug susceptibility testing as the initial test; however, current WHO guidelines recommend that when rifampicin resistance is detected by GeneXpert, further drug susceptibility testing should be performed to confirm resistance patterns and guide treatment. This includes testing for resistance to isoniazid, fluoroquinolones, and second-line injectables [22].

Alternative test(s)

Truenat technologies (Molbio Diagnostics, Goa, India) are rapid molecular assays that can detect tuberculosis (Truenat MTB and MTB Plus assays) and rifampicin resistance (Truenat MTB-RIF Dx assay) from sputum specimens, with results reported in less than

one hour [6]. Truenat MTB and MTB Plus assays use chip-based PCR for detection of *M tuberculosis* complex; if a result is positive, a sample of the already extracted DNA may be run on the chip-based Truenat MTB-RIF Dx assay to detect mutations associated with rifampicin resistance [6]. The assays use portable, battery-operated devices. WHO includes Truenat assays in the category 'molecular WHO-recommended rapid diagnostic tests that can detect tuberculosis (mWRD)' and recommends their use as follows [23].

- In adults and children with signs and symptoms of pulmonary tuberculosis, the Truenat MTB or MTB Plus may be used as an initial diagnostic test for tuberculosis rather than smear microscopy/culture (conditional recommendation, moderate certainty of evidence for test accuracy).
- In adults and children with signs and symptoms of pulmonary tuberculosis and a Truenat MTB or MTB Plus-positive result, Truenat MTB-RIF Dx may be used as an initial test for rifampicin resistance rather than culture and phenotypic drug susceptibility testing (conditional recommendation, very low certainty of evidence for test accuracy).

Additional alternative approaches for diagnosis of tuberculosis are still used extensively throughout the world. Alternatives include examination of smear 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 (no longer recommended by WHO for diagnosis but used for treatment monitoring). The sensitivity of smear microscopy ranges from 0% to 10% in children [24]. Examination of histology specimens under a microscope following a tissue biopsy targets acid-fast bacilli and granulomatous inflammation, frequently with caseous necrosis (necrotizing granulomas). However, these options are seldom pursued to diagnose tuberculosis in children 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 [25]. 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 [15, 25, 26]. One Cochrane review found that in inpatient settings, the use of lateral flow (LF)-LAM as part of a tuberculosis diagnostic testing strategy reduces mortality and probably results in a slight increase in tuberculosis treatment initiation in people with HIV [27]. WHO recommends the use of LF-LAM (Abbott Determine TB LAM Ag, Abbott Diagnostics, Chicago, IL, USA), the only product available at the time of this recommendation, to assist in the diagnosis of tuberculosis disease in HIV-positive adults, adolescents, and children. The full recommendations, which differ for inpatients and outpatients, are described in the WHO consolidated guidelines on tuberculosis (Module 3: diagnosis – rapid diagnostics for tuberculosis detection) [23]. However, the evidence for LF-LAM in children is limited and is primarily extrapolated from adults.

Line probe assays are a category of molecular tests for drug-resistant tuberculosis that offer speed of diagnosis (one or two days), standardized testing, and potential for high

throughput. Drawbacks are that line probe assays require skills and infrastructure only available in intermediate and central laboratories. Line probe assays for first-line drugs (which include rifampicin) include GenoType MTBDR_{plus} assay (MTBDR_{plus}, Bruker-Hain Lifescience, Nehren, Germany), and the Nipro NTM +MDRTB detection kit 2 (Nipro, Tokyo, Japan). These assays detect the presence of mutations associated with drug resistance to isoniazid and rifampicin. MTBDR_{plus} is the most widely studied line probe assay. WHO recommends that for people with a sputum smear-positive specimen or a culture isolate of *M. tuberculosis* complex, commercial molecular line probe assays may be used as the initial test instead of phenotypic drug susceptibility testing to detect resistance to rifampicin and isoniazid (conditional recommendation, moderate certainty in the evidence for the test's accuracy) [23]. Targeted next-generation sequencing (NGS) represents a new class of test for the detection of drug resistance to a broader list of drugs, and is recommended for drug resistance detection (conditional recommendation) [22].

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. Since the 2010s, unprecedented activity has focused on the development of new tools for the diagnosis of pulmonary and 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. *The Tuberculosis Diagnostics Pipeline Report: Advancing the Next Generation of Tools* describes tuberculosis tests in development [28].

Rationale

Timely and reliable diagnosis of tuberculosis in children remains challenging due to difficulties in collecting sputum samples and the paucibacillary nature of the disease. Underdiagnosis may lead to increased morbidity, mortality, and disease transmission in this key group.

This is an update of a Cochrane review first published in 2020 and previously updated in 2022. Our last update assessed the diagnostic accuracy of Xpert Ultra for pulmonary tuberculosis, tuberculosis meningitis, lymph node tuberculosis, and rifampicin resistance in children. Parts of the current review update were used to inform the 2024 update to the WHO guidelines for NAATs for detection of tuberculosis and drug-resistant tuberculosis (*yet to be published*; see Table 1).

OBJECTIVES

To assess the diagnostic accuracy of Xpert Ultra for detecting pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance in children (aged birth–9 years) with presumed tuberculosis.

Secondary objectives

- To investigate potential sources of heterogeneity in accuracy estimates. We considered age, comorbidity (HIV and severe malnutrition), and specimen type as potential sources.
- To summarize the frequency of Xpert Ultra trace results (trace represents detection of a very low quantity of *Mycobacterium tuberculosis* DNA).

METHODS

Differences between current update and previous versions of the review

Title

The title was changed for the 2022 update, from 'Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children' to 'Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children' [5].

Scope of the review

We considered guidance on when to update systematic reviews. An update is suggested if the question is relevant to decision making for practice, policy, or research priorities, or if the new data will change the findings or credibility of the original review [29]. WHO has redefined the age range for children as birth to nine years, as opposed to birth to 14 years. We updated our analysis to include children in the updated age range.

Objectives

The objectives were changed for the version published in 2022 [5].

Types of studies

We included abstracts with sufficient data to extract 2 × 2 tables for estimation of sensitivity and specificity.

Reference standard

We defined the microbiological reference standard as culture only and did not include sputum smear microscopy, which is less accurate. In addition, we clarified the reference standards. For stool, we accepted as a reference standard a positive result by Xpert Ultra in a sputum or gastric aspirate specimen, in addition to culture. For nasopharyngeal aspirates, we accepted a culture performed on a nasopharyngeal aspirate or a sputum specimen. For the composite reference standard, when information about tuberculosis treatment was unavailable, we accepted the frequently used research definition [30, 31]. In these situations, using the older definition [30], we defined tuberculosis as (1) confirmed, probable, and possible tuberculosis; and (2) non-tuberculosis. For the newer definition [31], we used the categories tuberculosis confirmed, unconfirmed, and unlikely. We also accepted study-specific definitions for the composite reference standard. We added targeted and whole genome sequencing as reference standards for rifampicin resistance.

Assessment of methodological quality

Using Quality Assessment of Studies of Diagnostic Accuracy – Revised (QUADAS-2), we judged all studies that evaluated stool using methods other than WHO-recommended methods (simple one step (SOS) or optimized sucrose flotation) as being of unclear concern.

Inconclusive results

We had planned to estimate the summary proportion of non-determinate Xpert Ultra results; however, there were few non-determinate results reported. We summarized these results in Table 2.

Criteria for considering studies for this review

Types of studies

We included cross-sectional studies and cohort studies from all settings (no restrictions on country where the study was conducted, World Bank income classification of the country, tuberculosis incidence, or laboratory service level). We included only studies from which we could extract or derive data on the index test giving true positives, false positives, true negatives, or false negatives, as assessed against the reference standards specified below (Reference standards). We included abstracts with sufficient data to extract 2 × 2 tables for estimation of sensitivity and specificity. We excluded diagnostic case-control studies and case reports.

Participants

We included studies that evaluated the index tests for pulmonary or extrapulmonary tuberculosis in children aged birth to nine years with presumed tuberculosis. Studies were eligible for inclusion if they described the use of Xpert Ultra in 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. In addition, we included studies evaluating stool specimens, because tuberculosis bacilli are present in swallowed sputum and are recoverable from stool samples using Xpert Ultra. We also included studies that assessed several different specimen types.

Index tests

The index test was Xpert Ultra.

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

- MTB (*M tuberculosis*) DETECTED HIGH; RIF (rifampicin) Resistance DETECTED
- MTB DETECTED MEDIUM; RIF Resistance DETECTED
- MTB DETECTED LOW; RIF Resistance DETECTED
- MTB DETECTED VERY LOW; RIF Resistance DETECTED
- MTB DETECTED HIGH; RIF Resistance NOT DETECTED
- MTB DETECTED MEDIUM; RIF Resistance NOT DETECTED
- MTB DETECTED LOW; RIF Resistance NOT DETECTED
- MTB DETECTED VERY LOW; RIF Resistance NOT DETECTED
- MTB DETECTED HIGH; RIF Resistance INDETERMINATE
- MTB DETECTED MEDIUM; RIF Resistance INDETERMINATE
- MTB DETECTED LOW; RIF Resistance INDETERMINATE
- MTB DETECTED VERY LOW; RIF Resistance INDETERMINATE
- MTB Trace DETECTED; RIF Resistance INDETERMINATE
- MTB NOT DETECTED
- INVALID (presence or absence of MTB cannot be determined)
- ERROR (presence or absence of MTB cannot be determined)
- NO RESULT (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* [32]. Although no rifampicin resistance results are available for people with trace results, a trace-positive result is sufficient to initiate tuberculosis therapy in children or people with HIV, according

to WHO [23]. Hence, we considered a trace result to mean *M tuberculosis* DETECTED.

Target conditions

The four target conditions were pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance.

Reference standards

For detection of pulmonary tuberculosis, tuberculous meningitis, and lymph node tuberculosis, we included two reference standards (see below regarding stool samples).

- Microbiological reference standard (MRS): tuberculosis was defined as a positive culture on solid or liquid medium from a respiratory sample.
- Composite reference standard (CRS): tuberculosis was defined as a positive culture (such as with MRS) 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.

For the CRS, in the absence of information on tuberculosis treatment, we accepted study-specific definitions (i.e. a standardized definition of tuberculosis provided by the primary study authors). We also accepted the uniform research definition [30, 31]. In these situations, for the older definition [30], we defined tuberculosis as 'confirmed, probable, and possible' and not tuberculosis as 'unlikely and not tuberculosis'. For the newer definition [31], we defined tuberculosis as 'confirmed and unconfirmed' and not tuberculosis as 'unlikely'.

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

Regarding stool specimens (used for the diagnosis of pulmonary tuberculosis), we defined the reference standard as culture or Xpert Ultra performed on a routine respiratory specimen, such as sputum or gastric aspirate specimen [33]. We did not include stool Xpert Ultra results in the definition of the reference standard. In addition, no 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 Ultra on a routine respiratory specimen. Regarding nasopharyngeal specimens, we included culture on a sputum specimen if a culture on a nasopharyngeal specimen was unavailable. This is because it is difficult to obtain the sample volume required for both Xpert Ultra and culture with a nasopharyngeal specimen alone.

For stool and nasopharyngeal 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 children, depending on disease severity, challenges of obtaining specimens, and resources [31]. Evaluation of multiple specimens, of the same or different types, may increase the yield of culture for confirming tuberculosis [14, 34]. 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 QUADAS-2 reference standard domain.

For rifampicin resistance, the reference standards were phenotypic drug susceptibility testing and targeted NGS or whole genome sequencing.

Search methods for identification of studies

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

Electronic searches

The Cochrane Infectious Diseases Group Information Specialist (VL) performed literature searches from 4 to 6 October 2023, without language restrictions, in the following databases, using the search terms described in [Supplementary material 1](#).

- Cochrane Central Register of Controlled Trials (CENTRAL), included in the Cochrane Library, issue 10, October 2023
- MEDLINE (Ovid)
- Embase (Ovid)
- Science Citation Index and Biosis previews (ISI Web of Knowledge)
- WHO Global Index Medicus
- SCOPUS (Elsevier)

VL also searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (<https://clinicaltrials.gov/>) and the WHO International Clinical Trials Registry platform (<https://trialsearch.who.int/>) to identify ongoing trials. Additionally, in July 2025, we checked in ClinicalTrials.gov whether active trials had been completed, and we checked in PubMed whether studies with unpublished data included in the analysis had since been published.

Searching other resources

The review authors examined the reference lists of included articles and relevant review articles identified through the electronic searches. VL also searched for relevant dissertations in ProQuest Dissertations & Theses A&I. We contacted researchers and experts in the field to identify additional eligible studies. The review authors searched for information on active studies (with available data but still recruiting) and unpublished studies from manufacturers through a WHO public call made between December 2023 and 15 February 2024, and from experts working on new diagnostics for tuberculosis such as STOP TB Partnership's New Diagnostic Working Group and FIND.

Data collection and analysis

We used the Cochrane data package for data collection and analysis ([Supplementary material 5](#)).

Selection of studies

We used Covidence to manage the selection of studies [35]. Two review authors (AWK and TN or MMM and PA) independently screened all titles and abstracts to eliminate studies that were clearly irrelevant. We then obtained the full-text articles of potentially eligible studies, and two review authors (AWK and TN or MMM and PA) independently assessed them against our predefined inclusion and exclusion criteria. We resolved disagreements by discussion. Owing to the need for data stratified by age and comorbidity, we contacted and requested data directly from the authors of all eligible reports and studies following full-text review. All available disaggregated data were included. We checked the included studies for errata and retractions. We recorded and summarized the reasons for excluding studies in [Supplementary material 3](#). We illustrated the study selection process in a PRISMA diagram [36].

Data extraction and management

We designed a data extraction form and piloted it on two included studies ([Supplementary material 6](#)). We then finalized the form based on the pilot test. Two review authors (AWK and MMM or TN and PA) independently extracted data using this data extraction form and discussed inconsistencies to achieve consensus. We consulted a third review author (AMM or KRS) to resolve discrepancies, as needed. We entered extracted data into Google sheets on password-protected computers. We secured the data set in a cloud storage workspace, and we stored extracted data for future review updates. Selected details of data extraction are listed below.

Study details

- Number of children after screening for exclusion and inclusion criteria
- Total number of children included in the analysis
- Specimen collection methods
- Unit of sample collection: one specimen, multiple specimens, unknown, unclear
- Target conditions: pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, rifampicin resistance
- Stage of the study at the time of data extraction for this review (e.g. recruitment completed, recruitment completed and data cleaned, or active and proportion of the target sample size recruited; see [Supplementary material 2](#))

Patient characteristics and setting

- Description of study population
- Age: median, mean, range
- Sex
- HIV status
- Percentage and number of children with and without HIV, if both were included in the study
- Type of respiratory specimen included: sputum, gastric aspirate or lavage, stool, nasopharyngeal aspirate
- Type of non-respiratory specimen included: CSF, fine-needle aspirate, lymph node biopsy, 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, inpatient, or both
- Description of radiographic findings
- Information on tuberculosis burden in the country

We classified countries as being high burden or not high burden for tuberculosis, HIV-associated tuberculosis, and multidrug/rifampicin-resistant tuberculosis based on the WHO classification for 2021 to 2025. A country may be classified as high burden for one, two, or all three categories.

We contacted the authors of all included studies for data on specific age ranges and subpopulations and for clarification on study characteristics.

Index test

- Pretreatment processing procedure for specimens used for Xpert Ultra
- Specimen condition: fresh, frozen, or both
- Numbers of true positives, false positives, false negatives, and true negatives by age group (birth to nine years; see example tables in [Supplementary material 7](#))
- Uninterpretable results for tuberculosis detection (invalid, error, or no result)
- Indeterminate results for detection of rifampicin resistance
- Xpert Ultra trace results

Reference standards

- Details of culture: solid or liquid
- MRS for stool specimens (culture or Xpert Ultra on sputum specimens)
- Composite reference standard
- Rifampicin resistance: phenotypic drug susceptibility testing or NGS or whole genome sequencing

For each target condition and specimen type, we considered one index test result per child. Hence, the primary unit of analysis was the child. If studies evaluated more than one specimen type, we extracted data for each specimen. Therefore, a single study could contribute 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 tool, which we adapted for this review [37].

The QUADAS-2 tool consists of four domains: patient selection, index test(s), reference standard(s), and flow and timing. All domains are assessed for risk of bias, and the first three domains are assessed 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. [Supplementary material 8](#) presents the QUADAS-2 tool with signalling questions tailored to this review. For bias in the patient selection domain, we assessed whether studies used consecutive/random sampling and avoided inappropriate exclusions. For applicability, we prioritized routine practice settings over tertiary centres. For the reference standard, we evaluated culture adequacy (multiple specimens vs single

specimen) and blinding. For flow/timing, we allowed up to seven days between tests and verified complete patient inclusion in analyses. [Supplementary material 9](#) presents a comprehensive list of signalling questions. Two review authors (AK and MM or TN and PA) independently completed QUADAS-2. We resolved any disagreements through discussion or by arbitration with a third review author (KRS or AMM), when necessary. We 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 [Supplementary material 2](#). We stratified all analyses by type of specimen and type of reference standard ([Supplementary material 4](#)). The unit of analysis was the individual participant for each index test (i.e. for a participant providing multiple specimens, only one sample was analysed for each specimen type). We presented individual study estimates of sensitivity and specificity graphically in forest plots using RevMan Web [38].

When data were sufficient, we performed meta-analyses to estimate summary sensitivities and specificities using a bivariate model [39, 40]. We used the bivariate model because the index test (Xpert Ultra) applies a common positivity criterion [41]. When we were unable to fit a bivariate model due to sparse data, few studies, or limited variability in specificity, we simplified the model to a univariate random-effects or fixed-effect logistic regression model to combine sensitivity and specificity separately, as appropriate given the observed data [42]. We performed meta-analyses using the metandi or meqrlogit commands for models that included random effects and the blogit command for fixed-effect meta-analyses in Stata version 18 [43]. Meta-analysis using univariate fixed-effect or random-effects logistic regression models is not possible when all studies in a meta-analysis report 100% specificity. For such analyses, we calculated summary specificity by dividing the total number of non-cases by the total number of true negatives, and we computed exact (Clopper-Pearson) 95% binomial confidence intervals (CIs) [44].

The summary estimates of sensitivity and specificity were used to compute positive and negative predictive values using prevalence levels suggested by the Global Programme on Tuberculosis and Lung Health. The prevalence values were 1%, 5%, and 10% for detection of tuberculosis and 2%, 10%, and 15% for detection of rifampicin resistance.

Approach to non-determinate and trace index test results

Non-determinate Xpert Ultra test results include 'Error', 'Invalid', and 'No Result', and may be due to an operator error, instrument, or cartridge issue. For each included study that reported the number of non-determinate results for tuberculosis detection, we estimated the proportion of non-determinate Xpert Ultra results. We had planned to estimate the summary proportion of non-determinate Xpert Ultra results. However, due to the small number of such results, the analysis was not possible. As recommended by WHO, we included trace results in the primary analyses as Xpert Ultra-positive results. For each included study that provided data on trace results, we calculated the percentage of test positives that were trace results (i.e. number of trace results/number of test positives).

Investigations of heterogeneity

We visually inspected forest plots and summary receiver operating characteristic curve (SROC) plots for heterogeneity. When data allowed, we evaluated sources of heterogeneity using subgroup analyses. We were unable to perform meta-regression because of the number of studies available. For tuberculosis detection, we performed subgroup analyses to investigate the influence of the following factors.

- Age group (< 1 year, 1–4 years, 5–9 years)
- HIV status (positive or negative)
- Severe malnutrition, defined as a Z-score below –3 standard deviations for weight-for-height, height-for-age, weight-for-age, or body mass index (BMI)

Sensitivity analyses

We performed sensitivity analyses including only data from published studies and from studies at low risk of bias.

We had planned to explore the effects of risk of bias items and study characteristics on summary estimates of Xpert Ultra accuracy by restricting the 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 children

However, we were unable to perform these sensitivity analyses because all studies satisfied the criteria or available data were insufficient.

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 [41].

Assessment of certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach for diagnostic studies [45, 46, 47]. As recommended, we rated the evidence certainty as high (not downgraded), moderate (downgraded one level), low (downgraded two levels), or very low (downgraded more than two levels) based on five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each outcome, the certainty of the evidence started as high when high-quality studies (cross-sectional or cohort studies) enrolled children with diagnostic uncertainty. For each domain, if we found a reason for downgrading, we used our judgement to classify the reason as serious (downgraded one level) or very serious (downgraded two levels).

Four review authors (AWK, TN, MMM, PA) discussed judgements and applied GRADE [48, 49].

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 (proportion) of the target condition in the included studies as a guide to whether there was indirectness in the population.

Inconsistency

GRADE recommends downgrading for unexplained inconsistency in sensitivity and specificity estimates. We carried out prespecified analyses to investigate potential sources of heterogeneity and downgraded when we could not explain inconsistency in accuracy estimates. We looked at the individual point estimates in the forest plots and judged whether they were sufficiently similar, as well as the CIs to see if they overlapped.

Imprecision

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

Publication bias

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

The summary of findings tables include the following details.

- The review question and its components, population, setting, index test, and reference standards
- Summary estimates of sensitivity and specificity with 95% CIs
- The number of included studies and children contributing to the estimates of sensitivity and specificity
- Prevalence values of the target condition with an explanation of why the values were chosen
- An assessment of the certainty of the evidence (GRADE)
- Explanations for downgrading, as needed

RESULTS

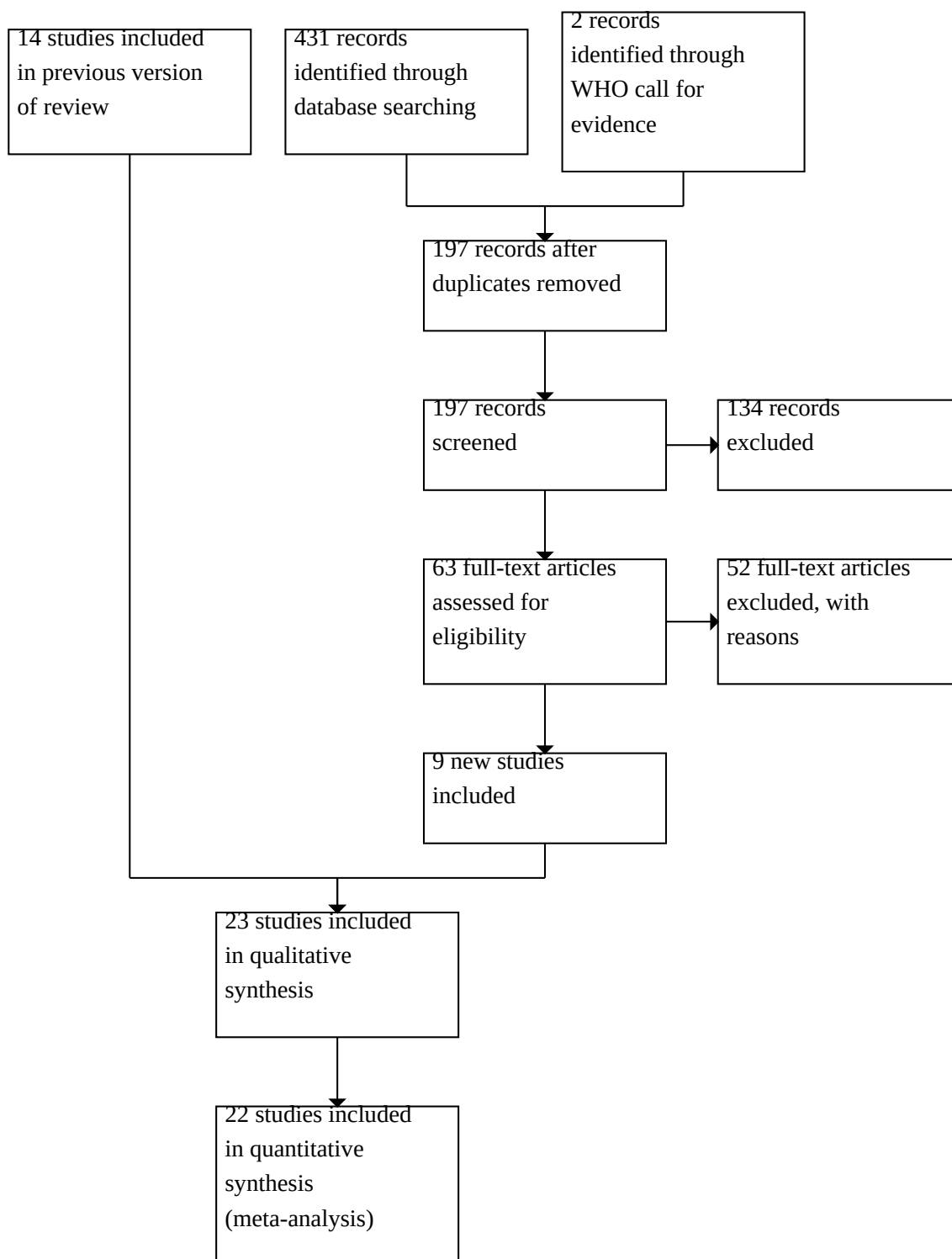
Results of the search

We identified 431 records through database searches conducted up to 6 October 2023, and we identified two further records through a WHO call for evidence. After removing duplicates, we screened 197 records by title and abstract. We excluded 134 of these, leaving 63 reports, which we retrieved for full text review. All studies were written in English. During the full-text review, we excluded 52 articles. Ultimately, nine new studies and 14 studies from the previous review were included, resulting in 23 studies included in the qualitative synthesis, and 22 studies included in the quantitative synthesis (meta-analysis). We found no studies with errata or retractions. All nine newly identified studies were included

in the quantitative synthesis. [Figure 2](#) shows the flow of studies in the review. We recorded the excluded studies (newly excluded and excluded in previous versions of this review [4, 5]), with reasons for their exclusion in [Supplementary material 3](#). We requested

disaggregated data from the authors of all included studies, and 14 of 35 (40%) of the study authors responded. In July 2025, all active studies had been completed, and there were no changes in published data.

Figure 2. Study flow diagram.



Description of included studies

[Supplementary material 2](#) and [Table 2](#) present key study characteristics. All were cross-sectional or cohort studies. No randomized controlled trials met our inclusion criteria. The included studies were conducted in both inpatient and outpatient settings. Seventeen studies took place in high-burden countries for tuberculosis, 16 in high-burden countries for tuberculosis/HIV, and 10 in high-burden countries for MDR tuberculosis. Three studies were conducted in high-income countries and 20 in low- and middle-income countries. Seventeen studies included children with HIV. All studies included a culture-based reference standard, and 13 included a composite definition for tuberculosis.

For pulmonary tuberculosis, 21 data sets (8186 children) were available for analysis; for rifampicin resistance in sputum specimens, three data sets (76 children) were available.

Regarding extrapulmonary tuberculosis, we identified three studies (215 children) that evaluated Xpert Ultra accuracy for tuberculous meningitis and two studies (58 children) evaluating lymph node tuberculosis. Additionally, three studies (37 children) evaluated pleural specimens, three studies (9 children) evaluated bone and joint specimens; one study (1 child) evaluated urine, and one study (10 children) evaluated tissue biopsies. Due to the small number of children with tuberculosis in these studies (< 5 cases per extrapulmonary tuberculosis site), meta-analysis was not appropriate.

Methodological quality of included studies

Pulmonary tuberculosis

[Figure 3](#) and [Figure 4](#) show risk of bias and applicability concerns for 23 studies that evaluated Xpert Ultra for detection of pulmonary or extrapulmonary tuberculosis. [Supplementary material 9](#) shows the methodological quality by reference standard and specimen type.

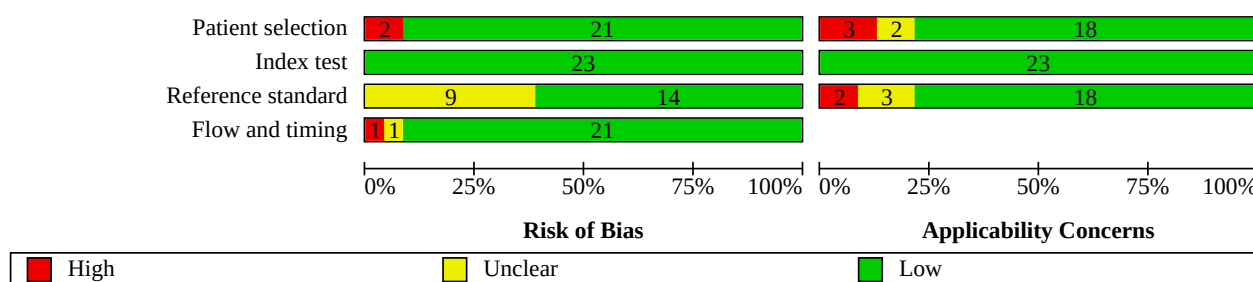
Figure 3. Risk of bias and applicability concerns summary: reviews authors' judgements about each domain for each included study. Judgements are based on the sputum specimen type, unless the study did not include sputum

specimens, in which case judgements are based on the specimen type listed: Aurilio 2022 (EPTB), Babo 2023 (stool), Chabala 2023 (GA), de Haas 2022 (stool), Lounnas 2025 (stool), Parigi 2021 (GA), Pradhan 2022 (EPTB)

| | Risk of Bias | | | | Applicability Concerns | | |
|----------------------|-------------------|------------|--------------------|-----------------|------------------------|------------|--------------------|
| | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Aguilera-Alonso 2022 | + | + | ? | + | - | + | + |
| Aurilio 2022 | + | + | ? | + | ? | + | + |
| Babo 2023 | + | + | ? | + | + | + | - |
| Barcellini 2019 | + | + | + | + | + | + | + |
| Chabala 2023 | + | + | + | + | + | + | + |
| Chibolela 2023 | + | + | ? | + | + | + | + |
| de Haas 2022 | + | + | ? | + | + | + | - |
| Enimil 2022 | - | + | ? | + | ? | + | + |
| Jaganath 2021 | + | + | + | + | + | + | + |
| Kabir 2020 | + | + | ? | + | - | + | ? |
| Khosa 2024 | + | + | + | + | + | + | + |
| Liu 2021 | - | + | + | - | + | + | ? |
| Lounnas 2025 | + | + | + | + | + | + | + |
| NCT04899076 | + | + | + | + | + | + | + |
| Nicol 2018 | + | + | + | + | + | + | + |
| Olbrich 2023 | + | + | + | + | + | + | + |
| Parigi 2021 | + | + | + | + | - | + | ? |
| Pradhan 2022 | + | + | ? | ? | + | + | + |
| Sabi 2018 | + | + | + | + | + | + | + |
| Sabi 2022 | + | + | ? | + | + | + | + |
| Ssengooba 2020 | + | + | + | + | + | + | + |
| Yenew 2023 | + | + | + | + | + | + | + |
| Zar 2018-2023 | + | + | + | + | + | + | + |

High
 Unclear
 Low

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.



Studies evaluating Xpert Ultra in sputum specimens (15 studies)

In the patient selection domain, we judged 13/15 studies (86.7%) at low risk of bias and 2/15 studies (13.3%) at high risk: Liu 2021 [50, 51] excluded children with definitive tuberculosis, and the method of patient selection in Enimil 2022 [52] was convenience sampling (not consecutive or random sampling). Regarding applicability, we judged 12/15 studies (80%) to be of low concern. We judged high concern for two studies (2/15, 13.3%) because children were enrolled exclusively as inpatients in tertiary care centres (Aguilera-Alonso 2022 [53]; Kabir 2020 [54]). We judged unclear concern for one study (1/15, 6.7%) because the setting was undefined (Enimil 2022).

In the index test domain, we judged all studies at low risk of bias because 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). Furthermore, the threshold for positivity is prespecified. Regarding applicability, we judged all 15 studies to be of low concern because they used standard protocols for Xpert Ultra testing of sputum.

In the reference standard domain, for MRS, we judged the risk of bias as low for 11/15 studies (73%), and unclear for four because they did not specify how many cultures were performed (Aguilera-Alonso 2022; Enimil 2022; Kabir 2020; Sabi 2022 [55]). Regarding applicability, for studies using culture, we assigned a low concern judgement for most (13/15, 86.7%) and unclear for two studies: Kabir 2020 only used solid culture, and it was unclear if Liu 2021 performed culture on sputum or gastric aspirate specimens. In the flow and timing domain, for MRS, we judged most studies (14/15, 93.8%) at low risk of bias and one study (1/15, 6.7%) at high risk because many children were excluded from the analysis (Liu 2021).

In the reference standard domain, for the CRS, we considered the risk of bias was low for 4/11 studies (36.4%); unclear for 3/11 studies (27.3%) because it was unclear if Xpert Ultra in respiratory specimens was included in the CRS (Aguilera-Alonso 2022; NCT04899076 [56]; Olbrich 2023 [57]), and high for 5/11 studies (45.5%) because Xpert Ultra in respiratory specimens was included in the CRS (Jaganath 2021 [58]; Kabir 2020; Khosa 2024 [59, 60]; Sabi 2022; Yenew 2023 [61, 62]).

Studies evaluating Xpert Ultra in gastric aspirate specimens (12 studies)

In the patient selection domain, we judged most studies (10/12, 83.3%) at low risk of bias and two studies (2/12, 16.6%) at high risk of bias: Enimil 2022 used convenience sampling, and Liu 2021 excluded children with definitive tuberculosis. We considered there were low applicability concerns for most studies (9/12, 75%), unclear concerns for one study (1/12, 8.3%) because the setting was undefined (Enimil 2022), and high concerns for two studies (2/12, 16.7%) because they enrolled only inpatients (Aguilera-Alonso 2022; Parigi 2021 [63]).

In the index test domain, we considered all 12 studies (100%) had low risk of bias and low compatibility concerns because of the standard method for processing Xpert Ultra in gastric specimens.

In the reference standard domain, for MRS, we judged 9/12 studies (75%) at low risk of bias because they used multiple cultures to verify pulmonary tuberculosis, and 3/12 studies (25%) at unclear risk because it was unclear if culture was performed on sputum or gastric aspirate specimens (Aguilera-Alonso 2022; Enimil 2022; Sabi 2022). Applicability concerns were low for most studies (10/12, 83.3%) and unclear for two studies: Liu 2021 performed cultures on sputum or gastric aspirate specimens, and Parigi 2021 did not specify the specimen type for culture. In the flow and timing domain, for MRS, we judged most studies (11/12, 91.7%) at low risk of bias and one study (1/12, 8.3%) at high risk because children were mostly excluded from the analysis (Liu 2021).

In the reference standard domain, for CRS, we judged 0/7 studies (0%) at low risk of bias, 2/7 studies (28.6%) at unclear risk, because it was unclear if Xpert Ultra in gastric aspirate was used in the CRS (Aguilera-Alonso 2022; Parigi 2021), and 5/7 studies (57.1%) at high risk because Xpert Ultra in gastric aspirate was used in the CRS (Jaganath 2021; Olbrich 2023; Sabi 2022; Yenew 2023), and children were mostly excluded from the analysis (Liu 2021).

Studies evaluating Xpert Ultra in nasopharyngeal specimens (7 studies)

In the patient selection domain, we judged most studies (6/7, 85.7%) at low risk of bias and one study (1/7, 14.3%) at high risk because it used convenience sampling and excluded most children from the analysis (Liu 2021). We considered applicability concerns were low for all studies.

In the index test domain, we judged all seven studies at low risk of bias because Xpert Ultra test results are automatically generated, the user is provided with printable test results (thus there is no room for subjective interpretation of test results), and the threshold for positivity is prespecified. We considered applicability concerns were low for all studies because they performed Xpert Ultra following product recommendations.

In the reference standard domain, for MRS, we judged all seven studies at low risk of bias. Applicability concerns were low for most studies (6/7, 85.7%) and unclear for one study (Liu 2021).

In the reference standard domain, for CRS, we judged one study (1/4, 25%) at low risk of bias and three studies (3/4, 75%) at unclear risk because it was unclear if Xpert Ultra in nasopharyngeal specimens was used in the CRS (Jaganath 2021; NCT04899076; Olbrich 2023).

Studies evaluating Xpert Ultra in stool specimens (10 studies)

In the patient selection domain, we judged most studies (9/10, 90%) at low risk of bias and one study (10%) at high risk because it excluded children with a definite diagnosis of tuberculosis (Liu 2021). We considered applicability concerns were low for most studies (8/10, 80%), high for one study (10%) because the children were exclusively inpatients in a tertiary/specialized hospital (Kabir 2020), and unclear for one study (10%) because the setting was undefined (Chibolela 2023 [64]).

In the index test domain, we judged all 10 studies at low risk of bias because Xpert Ultra test results are automatically generated, the user is provided with printable test results (thus there is no room for subjective interpretation of test results), and the threshold for positivity is prespecified. We considered there were low applicability concerns for most studies (8/10, 80%) and unclear concerns for two studies (20%) because the stool processing method was different from the SOS or optimized sucrose filtration method, or not described (NCT04899076).

In the reference standard domain, for MRS, we judged most studies (6/10, 70%) at low risk of bias because they used multiple cultures to verify tuberculosis. We judged the risk of bias as unclear for four studies (4/10, 40%) that only used Xpert Ultra in respiratory specimens as a reference standard and did not perform culture (Babo 2023 [65]; de Haas 2022 [66]) and two studies where only a single culture was performed (Chibolela 2023; Kabir 2020). We considered six studies (6/10, 60%) had low applicability concerns, two studies (2/10, 20%) had high concerns because they did not use culture as part of the reference standard, and two studies (2/10, 20%) had unclear concerns because the culture method was not specified or only solid culture was performed (Babo 2023; Kabir 2020). In the flow and timing domain, we judged most studies (9/10, 90%) at low risk of bias and one study (10%) at high risk because index and reference tests were not collected within the prespecified time period (Liu 2021).

In the reference standard domain, for CRS, we judged 2/5 studies (40%) at low risk of bias, 3/5 studies (40%) at unclear risk because it was unclear if they used Xpert Ultra on stool in the CRS (Chibolela 2023; de Haas 2022; NCT04899076), and 1/5 studies (20%) at high

risk because Xpert Ultra on stool was included in the CRS (Kabir 2020).

Rifampicin resistance

In the patient selection domain, we judged all three studies at low risk of bias (Aguilera-Alonso 2022; Olbrich 2023; Zar 2018-2023 [67]). Regarding applicability, in the patient selection domain, there were low applicability concerns for two studies (Olbrich 2023; Zar 2018-2023), and high concerns for one study because all children were recruited from an inpatient setting (Aguilera-Alonso 2022). In the index test, reference standard, and flow and timing domains, we judged all three studies at low risk of bias. The index test and reference standard had low applicability concerns.

Extrapulmonary tuberculosis

Tuberculous meningitis

Studies evaluating Xpert Ultra in cerebrospinal fluid specimens (3 studies)

In the patient selection and index test domains, we judged all three studies at low risk of bias (Olbrich 2023; Pradhan 2022 [68]; Zar 2018-2023). Regarding applicability, in the patient selection domain, there were low concerns for all three studies (Olbrich 2023; Pradhan 2022; Zar 2018-2023). In the reference test domain, we judged risk of bias as unclear for all three studies (Olbrich 2023; Pradhan 2022; Zar 2018-2023). In the flow and timing domain, we judged one study at unclear risk of bias (Pradhan 2022) and two studies at low risk (Olbrich 2023; Zar 2018-2023). We considered there were low applicability concerns in all studies for the patient selection, index test, and reference standard domains.

Lymph node tuberculosis

Studies evaluating Xpert Ultra in lymph node tissue and aspirate specimens (2 studies)

In the patient selection and index test domains, we judged both studies at low risk of bias (Aurilio 2022 [69]; Zar 2018-2023). Regarding applicability, in the patient selection domain, we considered one study had low applicability concerns (Zar 2018-2023), and one study had unclear concerns (Aurilio 2022). In the reference test domain, we judged both studies at unclear risk of bias (Aurilio 2022; Zar 2018-2023). In the flow and timing domain, we judged both studies at low risk of bias (Aurilio 2022; Zar 2018-2023). We judged both studies as having low applicability concerns for the index test and reference standard domains. One study had unclear applicability in the patient selection domain (Aurilio 2022).

Findings

Detection of pulmonary tuberculosis

Due to low variability in specificity and in the volume of analyses, we chose to present only forest plots, as they are more informative than the corresponding SROC plots.

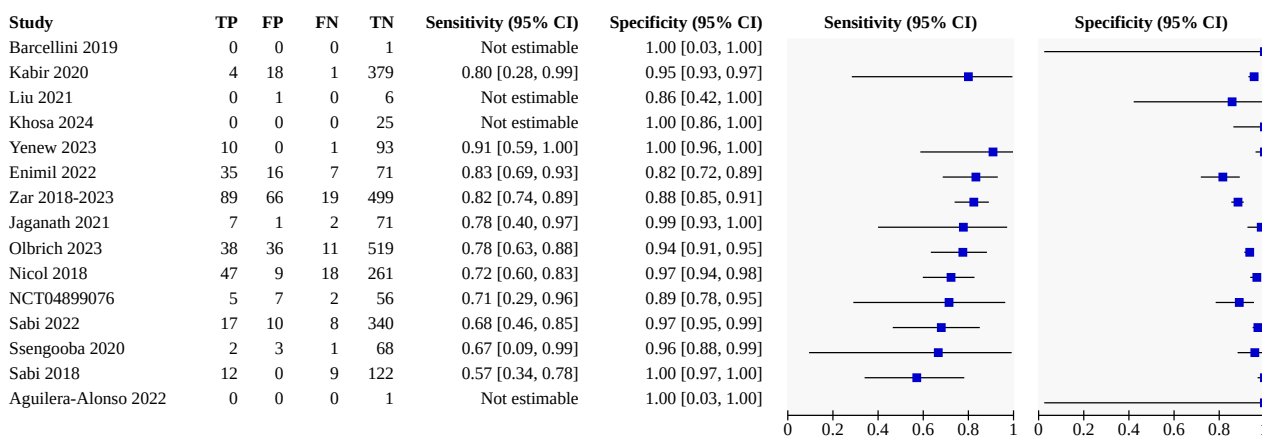
Xpert Ultra for pulmonary tuberculosis

Figure 5 shows individual sensitivity and specificity values for each study according to type of specimen and reference standard. Table 3 shows the summary sensitivity and specificity values for pulmonary tuberculosis by type of specimen.

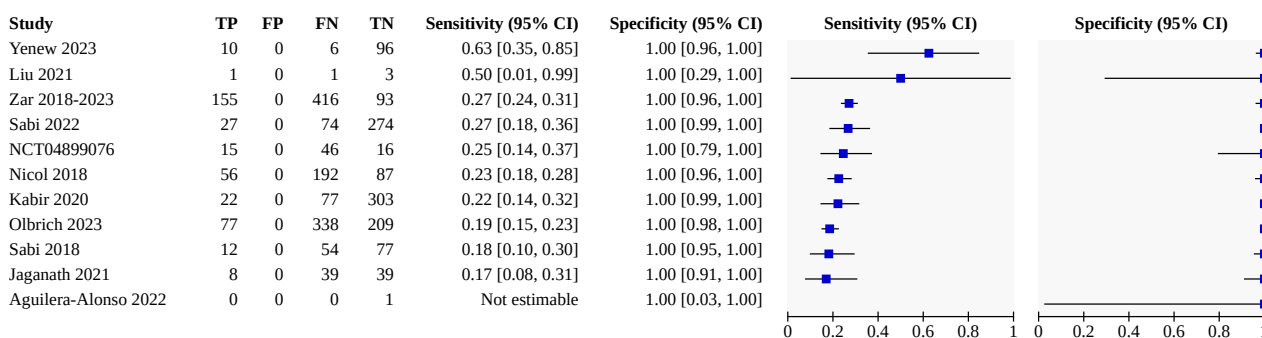
Figure 5. Forest plots of Xpert Ultra sensitivity and specificity for diagnosis of pulmonary tuberculosis in children in all specimen types and against all reference standards. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

FN: false negative; FP: false positive; TN: true negative; TP: true positive. For stool specimens, microbiological reference standard is used because Xpert on sputum specimens was included in the reference standard.

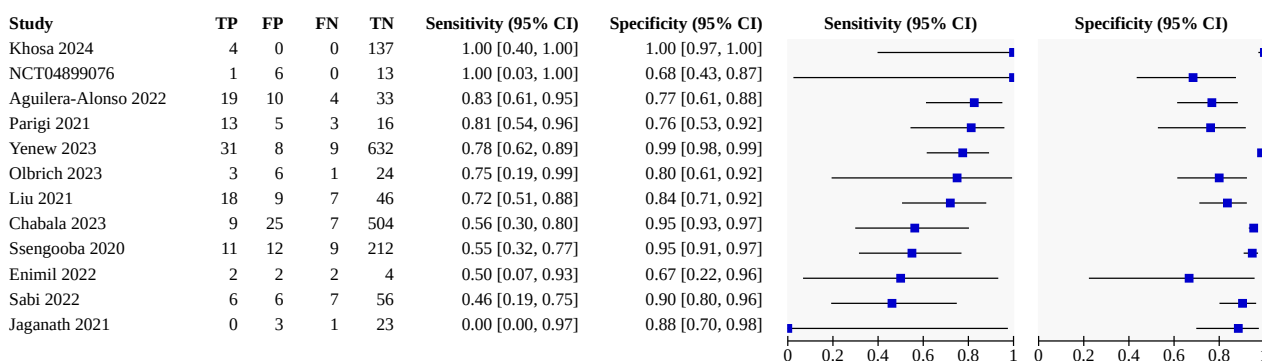
Xpert Ultra, sputum, 0–9 years, culture



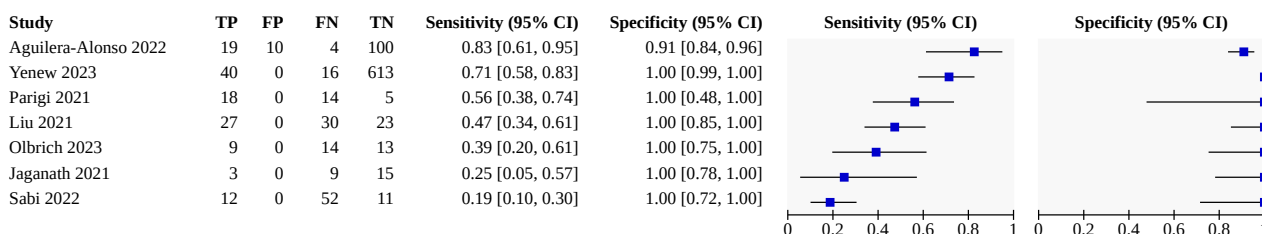
Xpert Ultra, sputum, 0–9 years, composite reference standard



Xpert Ultra, gastric aspirate, 0–9 years, culture



Xpert Ultra, gastric aspirate, 0–9 years, composite reference standard



Xpert Ultra, stool, 0–9 years, microbiological reference standard

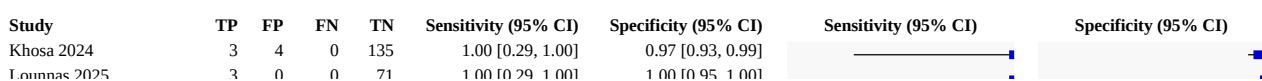
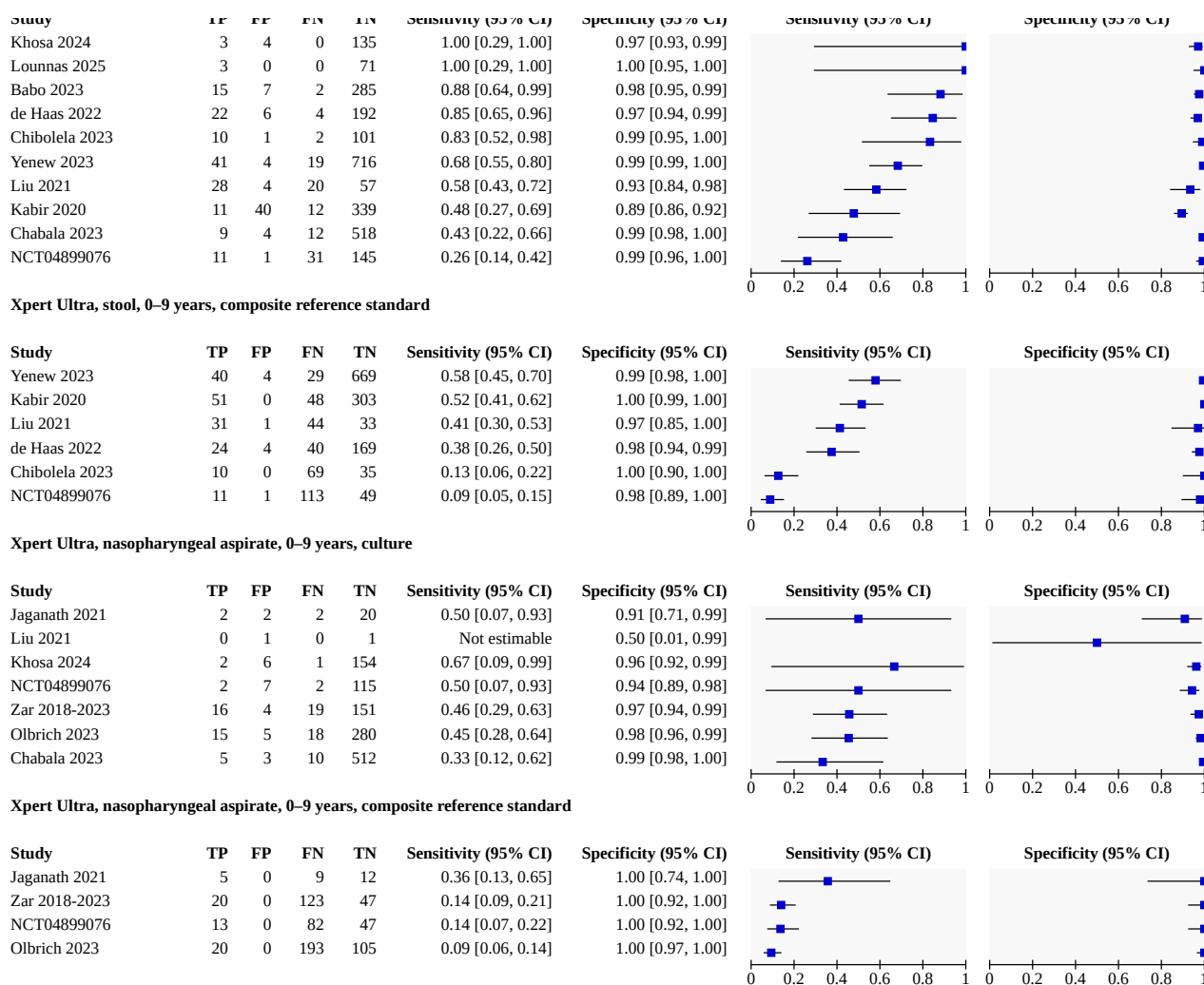


Figure 5. (Continued)

**Xpert Ultra in sputum specimens****Microbiological reference standard**

Fifteen studies (3024 children) evaluated sputum against an MRS (Aguilera-Alonso 2022; Barcellini 2019 [70]; Enimil 2022; Jaganath 2021; Kabir 2020; Khosa 2024; Liu 2021; NCT04899076; Nicol 2018 [71]; Olbrich 2023; Sabi 2018 [72]; Sabi 2022; Ssengooba 2020 [73]; Yenew 2023; Zar 2018-2023). Sensitivities ranged from 57% to 91% and specificities from 82% to 100%. Eleven studies (2990 children) contributed to the meta-analysis. The summary sensitivity was 75.3% (95% CI 68.9% to 80.8%), and the summary specificity was 95.9% (95% CI 92.3% to 97.9%).

Composite reference standard

Eleven studies (2824 children) evaluated sputum against a CRS (Aguilera-Alonso 2022; Jaganath 2021; Kabir 2020; Liu 2021; Olbrich 2023; NCT04899076; Nicol 2018; Sabi 2018; Sabi 2022; Yenew 2023; Zar 2018-2023). Sensitivities ranged from 17% to 63%, and specificities were all 100%. Ten studies (2823 children) contributed to the meta-analysis. The summary sensitivity was 23.5% (95% CI 20.3% to 27.0%), and the summary specificity was 100.0% (95% CI 99.7% to 100.0%).

Xpert Ultra in gastric aspirate specimens**Microbiological reference standard**

Twelve studies (1959 children) evaluated gastric aspirate against an MRS (Aguilera-Alonso 2022; Chabala 2023 [74, 75]; Enimil 2022; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Parigi 2021; Sabi 2022; Ssengooba 2020; Yenew 2023). Sensitivities ranged from 0% to 100% and specificities from 67% to 100%. All 12 studies contributed to the meta-analysis. The summary sensitivity was 69.6% (95% CI 60.3% to 77.6%), and the summary specificity was 91.0% (95% CI 82.5% to 95.6%).

Composite reference standard

Seven studies (1057 children) evaluated gastric aspirate against a CRS (Aguilera-Alonso 2022; Jaganath 2021; Liu 2021; Olbrich 2023; Parigi 2021; Sabi 2022; Yenew 2023). Sensitivities ranged from 19% to 83% and specificities from 91% to 100%. All seven studies contributed to the meta-analysis. The summary sensitivity was 48.8% (95% CI 31.4% to 63.7%), and the summary specificity was 98.7% (95% CI 97.7% to 99.3%).

Xpert Ultra in stool specimens**Microbiological reference standard**

Ten studies (2885 children) evaluated Xpert Ultra in stool specimens against an MRS (Babo 2023; Chabala 2023; Chibolela 2023; de Haas 2022; Kabir 2020; Liu 2021; Khosa 2024; Lounnas 2025 [76, 77]; NCT04899076; Yenew 2023). Sensitivities ranged from 26% to 100% and specificities from 89% to 100%. All studies contributed to the meta-analysis. The summary sensitivity was 68.0% (95% CI 50.3% to 81.7%), and the summary specificity was 98.2% (95% CI 96.3% to 99.1%).

Composite reference standard

Six studies (1778 children) evaluated Xpert Ultra in stool specimens against a composite reference standard (Chibolela 2023; de Haas 2022; Kabir 2020; Liu 2021; NCT04899076; Yenew 2023). Sensitivities ranged from 9% to 58% and specificities from 97% to 100%. All studies contributed to the meta-analysis. The summary sensitivity was 31.4% (95% CI 17.2% to 50.2%), and the summary specificity was 99.0% (95% CI 97.4% to 99.6%).

Xpert Ultra in nasopharyngeal aspirate specimens**Microbiological reference standard**

Seven studies (1355 children) evaluated nasopharyngeal aspirate against an MRS (Chabala 2023; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Zar 2018-2023). Sensitivities ranged from 33% to 67% and specificities from 50% to 99%. Six studies (1353 children) contributed to the meta-analysis. The

summary sensitivity was 46.2% (95% CI 34.9% to 57.9%), and the summary specificity was 97.5% (95.1% to 98.7%).

Composite reference standard

Four studies (676 children) evaluated nasopharyngeal aspirate against a CRS (Jaganath 2021; NCT04899076; Olbrich 2023; Zar 2018-2023). Sensitivities ranged from 9% to 36%, and specificities were all 100%. All studies contributed to the meta-analysis. The summary sensitivity was 12.7% (95% CI 9.2% to 17.3%), and the summary specificity was 100.0% (95% CI 98.3% to 100.0%).

Investigations of heterogeneity

Overall, specificity estimates were consistently high across studies, and heterogeneity was low. Nonetheless, the heterogeneity of sensitivity is moderate from studies for each specimen type and reference standard, likely due to the inclusion of several small studies with wide CIs. We performed subgroup analyses to investigate potential sources of this heterogeneity. The results for MRS and CRS are presented in Table 4 and Table 5; for brevity, we have summarized the MRS results below.

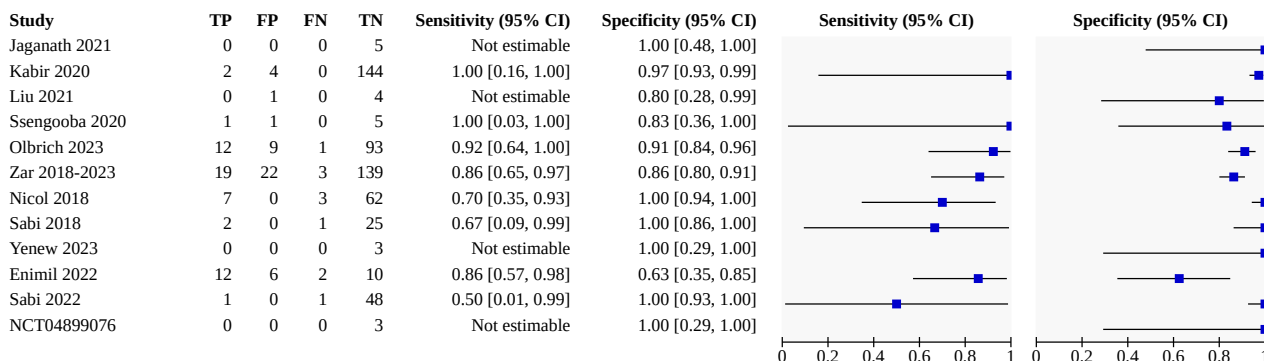
Xpert Ultra accuracy by specimen type and age group

The analyses for Xpert Ultra sensitivity and specificity by specimen type and age group are based on a small number of studies. Sensitivity and specificity estimates for individual studies are presented in Figure 6 (sputum and gastric aspirate) and Figure 7 (stool and nasopharyngeal aspirate). Table 4 presents summary sensitivity and specificity estimates by specimen type and age group.

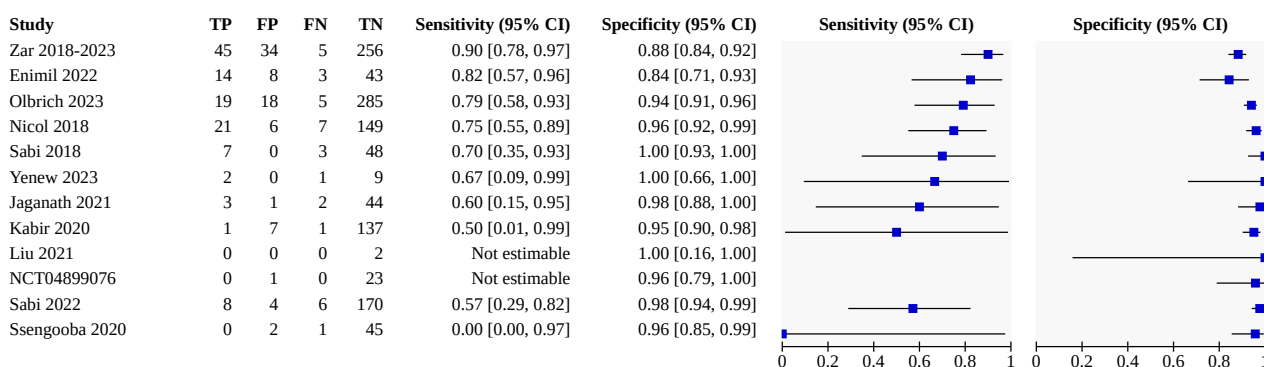
Figure 6. Forest plots of Xpert Ultra sensitivity and specificity in sputum and gastric aspirate for pulmonary tuberculosis by age group, all with culture reference standard. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

FN: false negative; FP: false positive; TN: true negative; TP: true positive.

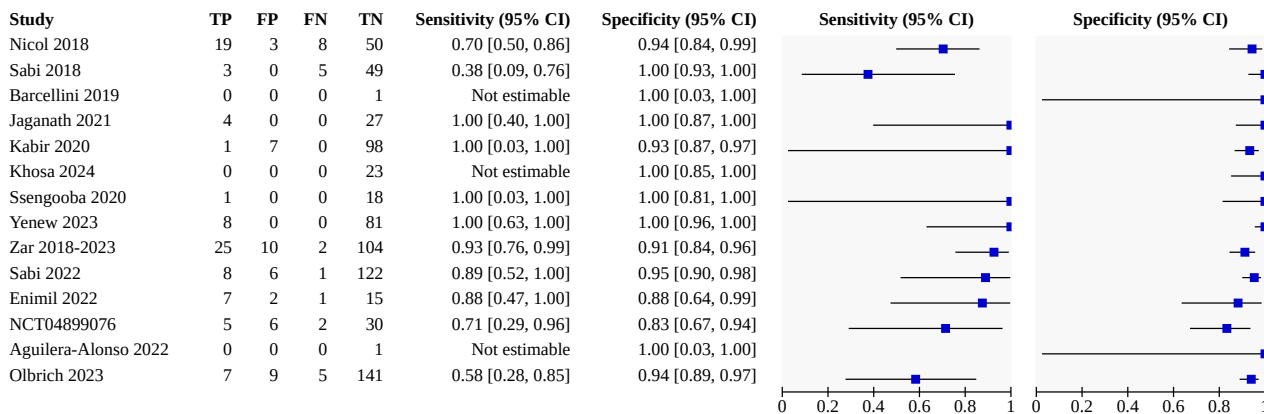
Xpert Ultra, sputum, < 1 year, culture



Xpert Ultra, sputum, 1–4 years, culture



Xpert Ultra, sputum, 5–9 years, culture



Xpert Ultra, gastric aspirate, < 1 year, culture

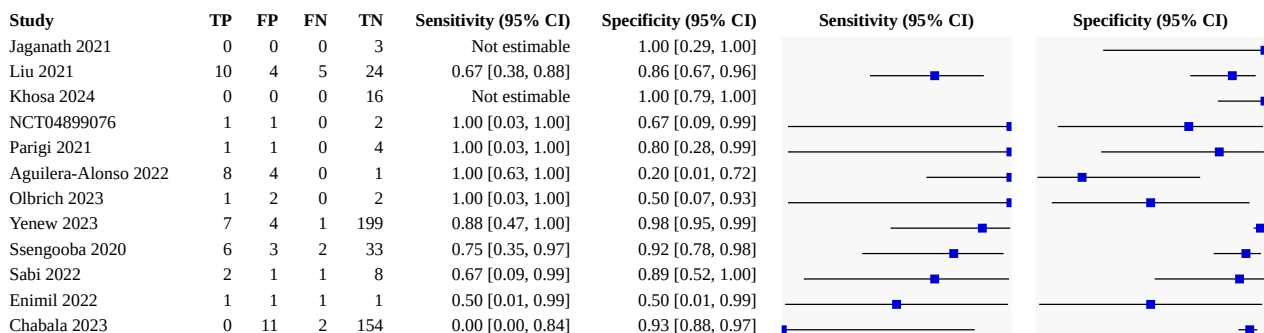


Figure 6. (Continued)

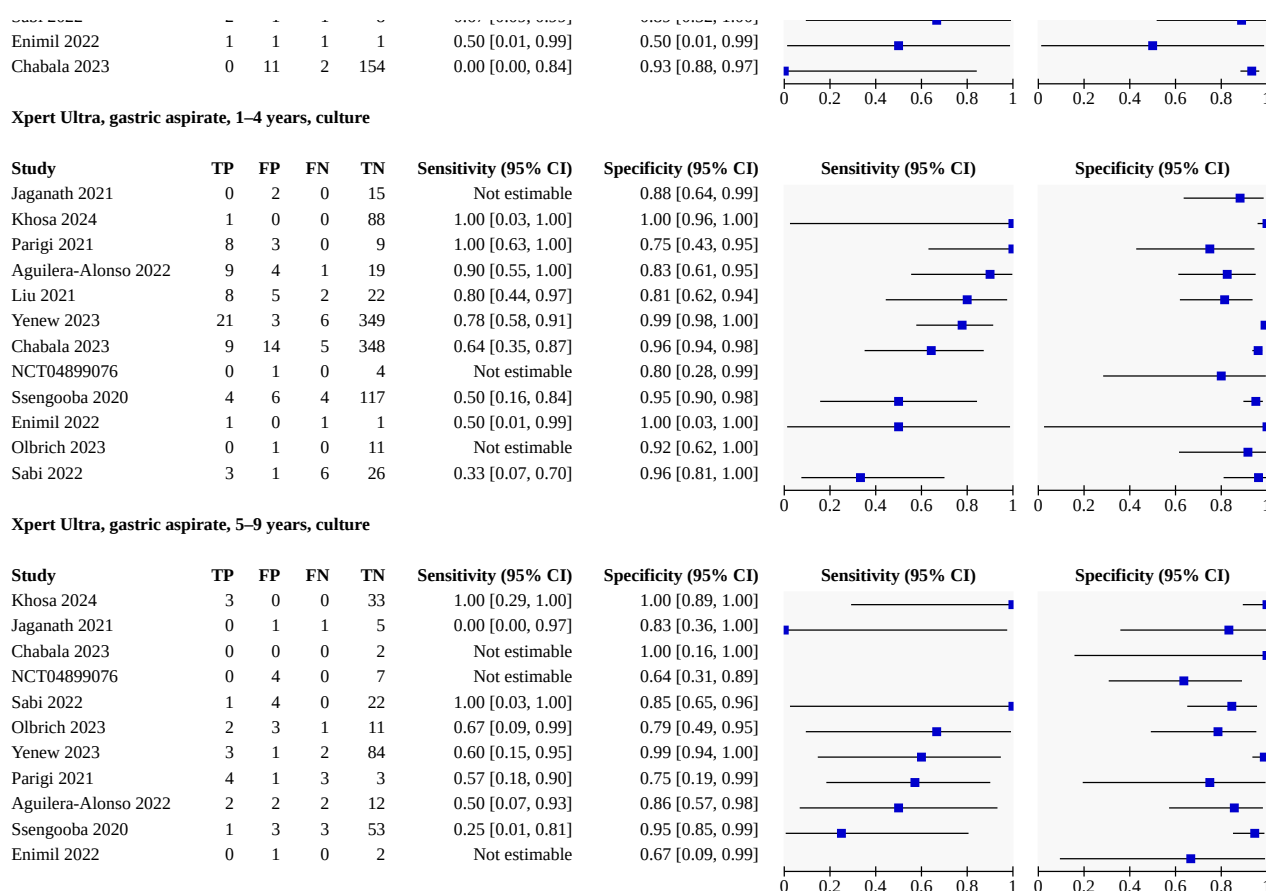
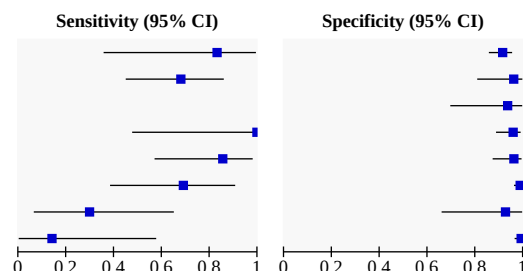


Figure 7. Forest plots of Xpert Ultra sensitivity and specificity in stool and nasopharyngeal specimens for pulmonary tuberculosis by age group, all with microbiological reference standard. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

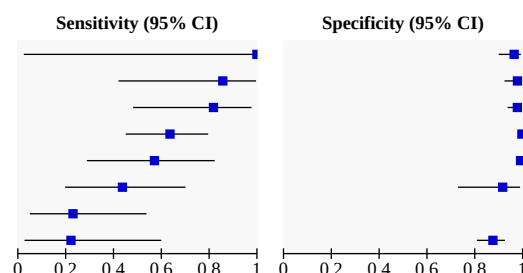
FN: false negative; FP: false positive; TN: true negative; TP: true positive. For stool specimens, microbiological reference standard is used because Xpert on sputum specimens was included in the reference standard.

Xpert Ultra, stool, < 1 year, microbiological reference standard

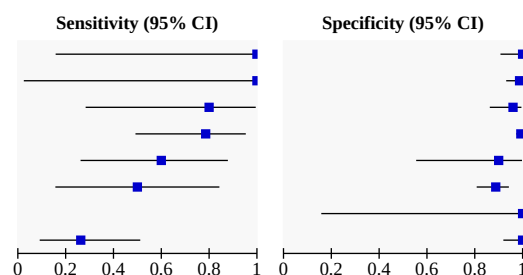
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|
| Kabir 2020 | 5 | 12 | 1 | 132 | 0.83 [0.36, 1.00] | 0.92 [0.86, 0.96] |
| Liu 2021 | 15 | 1 | 7 | 26 | 0.68 [0.45, 0.86] | 0.96 [0.81, 1.00] |
| Khosa 2024 | 0 | 1 | 0 | 15 | Not estimable | 0.94 [0.70, 1.00] |
| Babo 2023 | 5 | 3 | 0 | 73 | 1.00 [0.48, 1.00] | 0.96 [0.89, 0.99] |
| de Haas 2022 | 12 | 2 | 2 | 53 | 0.86 [0.57, 0.98] | 0.96 [0.87, 1.00] |
| Yenew 2023 | 9 | 2 | 4 | 196 | 0.69 [0.39, 0.91] | 0.99 [0.96, 1.00] |
| NCT04899076 | 3 | 1 | 7 | 13 | 0.30 [0.07, 0.65] | 0.93 [0.66, 1.00] |
| Chabala 2023 | 1 | 1 | 6 | 164 | 0.14 [0.00, 0.58] | 0.99 [0.97, 1.00] |

**Xpert Ultra, stool, 1–4 years, microbiological reference standard**

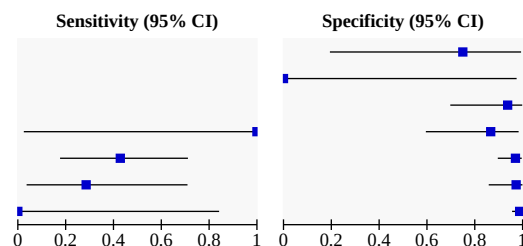
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|
| Khosa 2024 | 1 | 3 | 0 | 82 | 1.00 [0.03, 1.00] | 0.96 [0.90, 0.99] |
| de Haas 2022 | 6 | 2 | 1 | 91 | 0.86 [0.42, 1.00] | 0.98 [0.92, 1.00] |
| Babo 2023 | 9 | 3 | 2 | 134 | 0.82 [0.48, 0.98] | 0.98 [0.94, 1.00] |
| Yenew 2023 | 21 | 1 | 12 | 349 | 0.64 [0.45, 0.80] | 1.00 [0.98, 1.00] |
| Chabala 2023 | 8 | 3 | 6 | 352 | 0.57 [0.29, 0.82] | 0.99 [0.98, 1.00] |
| Liu 2021 | 7 | 2 | 9 | 22 | 0.44 [0.20, 0.70] | 0.92 [0.73, 0.99] |
| NCT04899076 | 3 | 0 | 10 | 0 | 0.23 [0.05, 0.54] | Not estimable |
| Kabir 2020 | 2 | 17 | 7 | 120 | 0.22 [0.03, 0.60] | 0.88 [0.81, 0.93] |

**Xpert Ultra, stool, 5–9 years, microbiological reference standard**

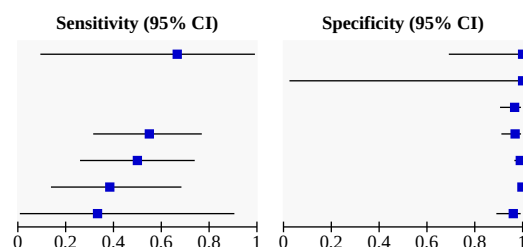
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|
| Khosa 2024 | 2 | 0 | 0 | 38 | 1.00 [0.16, 1.00] | 1.00 [0.91, 1.00] |
| Babo 2023 | 1 | 1 | 0 | 78 | 1.00 [0.03, 1.00] | 0.99 [0.93, 1.00] |
| de Haas 2022 | 4 | 2 | 1 | 48 | 0.80 [0.28, 0.99] | 0.96 [0.86, 1.00] |
| Yenew 2023 | 11 | 2 | 3 | 271 | 0.79 [0.49, 0.95] | 0.99 [0.97, 1.00] |
| Liu 2021 | 6 | 1 | 4 | 9 | 0.60 [0.26, 0.88] | 0.90 [0.55, 1.00] |
| Kabir 2020 | 4 | 11 | 4 | 87 | 0.50 [0.16, 0.84] | 0.89 [0.81, 0.94] |
| Chabala 2023 | 0 | 0 | 0 | 2 | Not estimable | 1.00 [0.16, 1.00] |
| NCT04899076 | 5 | 0 | 14 | 44 | 0.26 [0.09, 0.51] | 1.00 [0.92, 1.00] |

**Xpert Ultra, nasopharyngeal aspirate, < 1 year, culture**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|-----|----------------------|----------------------|
| Jaganath 2021 | 0 | 1 | 0 | 3 | Not estimable | 0.75 [0.19, 0.99] |
| Liu 2021 | 0 | 1 | 0 | 0 | Not estimable | 0.00 [0.00, 0.97] |
| Khosa 2024 | 0 | 1 | 0 | 15 | Not estimable | 0.94 [0.70, 1.00] |
| NCT04899076 | 1 | 2 | 0 | 13 | 1.00 [0.03, 1.00] | 0.87 [0.60, 0.98] |
| Olbrich 2023 | 6 | 2 | 8 | 65 | 0.43 [0.18, 0.71] | 0.97 [0.90, 1.00] |
| Zar 2018-2023 | 2 | 1 | 5 | 36 | 0.29 [0.04, 0.71] | 0.97 [0.86, 1.00] |
| Chabala 2023 | 0 | 2 | 2 | 160 | 0.00 [0.00, 0.84] | 0.99 [0.96, 1.00] |

**Xpert Ultra, nasopharyngeal aspirate, 1–4 years, culture**

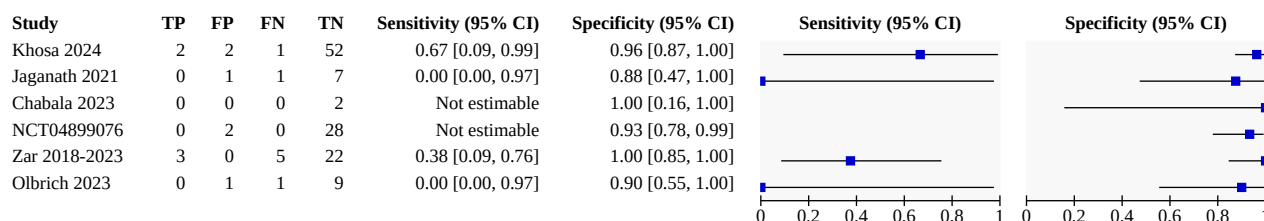
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|-----|----------------------|----------------------|
| Jaganath 2021 | 2 | 0 | 1 | 10 | 0.67 [0.09, 0.99] | 1.00 [0.69, 1.00] |
| Liu 2021 | 0 | 0 | 0 | 1 | Not estimable | 1.00 [0.03, 1.00] |
| Khosa 2024 | 0 | 3 | 0 | 87 | Not estimable | 0.97 [0.91, 0.99] |
| Zar 2018-2023 | 11 | 3 | 9 | 93 | 0.55 [0.32, 0.77] | 0.97 [0.91, 0.99] |
| Olbrich 2023 | 9 | 2 | 9 | 206 | 0.50 [0.26, 0.74] | 0.99 [0.97, 1.00] |
| Chabala 2023 | 5 | 1 | 8 | 350 | 0.38 [0.14, 0.68] | 1.00 [0.98, 1.00] |
| NCT04899076 | 1 | 3 | 2 | 74 | 0.33 [0.01, 0.91] | 0.96 [0.89, 0.99] |

**Xpert Ultra, nasopharyngeal aspirate, 5–9 years, culture**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|------------|----|----|----|----|----------------------|----------------------|
| Khosa 2024 | 2 | 2 | 1 | 52 | 0.67 [0.09, 0.99] | 0.96 [0.87, 1.00] |



Figure 7. (Continued)

**Sputum specimens, age under one year**

Twelve studies (651 children) evaluated Xpert Ultra in sputum against an MRS in children aged under one year (Enimil 2022; Jaganath 2021; Kabir 2020; Liu 2021; NCT04899076; Nicol 2018; Olbrich 2023; Sabi 2018; Sabi 2022; Ssengooba 2020; Yenew 2023; Zar 2018-2023). Four studies contributed no data to the meta-analysis because sensitivity was not estimable (Jaganath 2021; Liu 2021; NCT04899076; Yenew 2023). In the remaining eight studies (635 children), Xpert Ultra summary sensitivity was 81.7% (95% CI 67.8% to 90.4%), and summary specificity was 96.3% (95% CI 85.1% to 99.2%).

Sputum specimens, age one to four years

Twelve studies (1446 children) evaluated Xpert Ultra on sputum against an MRS in children aged one to four years (Enimil 2022; Jaganath 2021; Kabir 2020; Liu 2021; NCT04899076; Nicol 2018; Olbrich 2023; Sabi 2018; Sabi 2022; Ssengooba 2020; Yenew 2023; Zar 2018-2023). Two studies contributed no data to the meta-analysis because sensitivity was not estimable (Liu 2021; NCT04899076). In the remaining 10 studies (1420 children), Xpert Ultra summary sensitivity was 74.6% (95% CI 63.1% to 83.4%), and summary specificity was 95.3% (95% CI 92.3% to 97.2%).

Sputum specimens, age five to nine years

Fourteen studies (915 children) evaluated Xpert Ultra on sputum against an MRS in children aged five to nine years (Aguilera-Alonso 2022; Barcellini 2019; Enimil 2022; Jaganath 2021; Kabir 2020; Khosa 2024; Nicol 2018; Olbrich 2023; Sabi 2018; Sabi 2022; Ssengooba 2020; Yenew 2023; Zar 2018-2023). Three studies contributed no data to the meta-analysis because sensitivity was not estimable (Aguilera-Alonso 2022; Barcellini 2019; Khosa 2024). In the remaining 11 studies (890 children), Xpert Ultra summary sensitivity was 81.9% (95% CI 65.3% to 91.6%), and summary specificity was 95.4% (95% CI 91.6% to 97.6%).

Gastric aspirate specimens, age under one year

Twelve studies (528 children) evaluated Xpert Ultra in gastric aspirate specimens against an MRS in children aged under one year (Aguilera-Alonso 2022; Chabala 2023; Enimil 2022; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Parigi 2021; Sabi 2022; Ssengooba 2020; Yenew 2023). Two studies contributed no data to the meta-analysis because sensitivity was not estimable (Jaganath 2021; Khosa 2024). In the remaining 10 studies (509 children), Xpert Ultra summary sensitivity was 77.2% (95% CI 59.3% to 88.7%), and summary specificity was 84.4% (95% CI 66.2% to 93.7%).

Gastric aspirate specimens, age one to four years

Twelve studies (1104 children) evaluated Xpert Ultra in gastric aspirate specimens against an MRS in children aged one to four years (Aguilera-Alonso 2022; Chabala 2023; Enimil 2022; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Parigi 2021; Sabi 2022; Ssengooba 2020; Yenew 2023). Three studies contributed no data to the meta-analysis because sensitivity was not estimable (Jaganath 2021; NCT04899076; Olbrich 2023). In the remaining nine studies (1104 children), Xpert Ultra summary sensitivity was 72.8% (95% CI 55.4% to 85.3%), and summary specificity was 95.6% (95% CI 88.8% to 98.4%).

Gastric aspirate specimens, age five to nine years

Eleven studies (282 children) evaluated Xpert Ultra in gastric aspirate specimens against an MRS in children aged five to nine years (Aguilera-Alonso 2022; Chabala 2023; Enimil 2022; Jaganath 2021; Khosa 2024; NCT04899076; Olbrich 2023; Parigi 2021; Sabi 2022; Ssengooba 2020; Yenew 2023). Three studies contributed no data to the meta-analysis because sensitivity was not estimable (Chabala 2023; Enimil 2022; NCT04899076). In the remaining eight studies (266 children), Xpert Ultra summary sensitivity was 56.8% (95% CI 38.0% to 73.9%), and summary specificity was 93.0% (95% CI 84.3% to 97.0%).

Stool specimens, age under one year

Nine studies (787 children) evaluated Xpert Ultra in stool against an MRS in children aged under one year (Babo 2023; Chabala 2023; de Haas 2022; Kabir 2020; Khosa 2024; Liu 2021; NCT04899076; Lounnas 2025; Yenew 2023). One study contributed no data to the meta-analysis because sensitivity was not estimable. In the remaining eight studies (771 children), Xpert Ultra summary sensitivity was 71.6% (95% CI 45.3% to 88.5%), and summary specificity was 97.0% (95% CI 93.7% to 98.6%).

Stool specimens, age one to four years

Eight studies (1364 children) evaluated Xpert Ultra in stool against an MRS in children aged one to four years (Babo 2023; Chabala 2023; de Haas 2022; Kabir 2020; Khosa 2024; Liu 2021; NCT04899076; Yenew 2023). One study contributed no data to the meta-analysis because specificity was not estimable (NCT04899076). In the remaining seven studies (1351 children), Xpert Ultra summary sensitivity was 57.9% (95% CI 44.6% to 70.3%), and summary specificity was 98.1% (95% CI 95.3% to 99.3%).

Stool specimens, age five to nine years

Eight studies (653 children) evaluated Xpert Ultra in stool against an MRS in children aged five to nine years (Babo 2023; Chabala 2023; de Haas 2022; Kabir 2020; Khosa 2024; Liu 2021; NCT04899076; Yenew 2023).

2023). One study contributed no data to the meta-analysis because sensitivity was not estimable (Chabala 2023). In the remaining seven studies (575 children), Xpert Ultra summary sensitivity was 62.9% (95% CI 39.5% to 81.5%), and summary specificity was 98.0% (95% CI 93.9% to 99.4%).

Nasopharyngeal aspirate specimens, age under one year

Seven studies (326 children) evaluated Xpert Ultra in gastric aspirate specimens against an MRS in children aged under one year (Chabala 2023; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Zar 2018-2023). Meta-analysis was not possible due to the low number of total cases (24 cases).

Nasopharyngeal aspirate specimens, age one to four years

Seven studies (890 children) evaluated Xpert Ultra in gastric aspirate specimens against an MRS in children aged one to four years (Chabala 2023; Jaganath 2021; Khosa 2024; Liu 2021; NCT04899076; Olbrich 2023; Zar 2018-2023). Two studies contributed no data to the meta-analysis because sensitivity was not estimable (Khosa 2024; Liu 2021). In the remaining five studies

(799 children), Xpert Ultra summary sensitivity was 49.3% (95% CI 36.2% to 62.5%), and summary specificity was 98.7% (95% CI 96.6% to 99.5%).

Nasopharyngeal aspirate specimens, age five to nine years

Six studies (139 children) evaluated Xpert Ultra in gastric aspirate specimens against culture in children aged five to nine years (Chabala 2023; Jaganath 2021; Khosa 2024; NCT04899076; Olbrich 2023; Zar 2018-2023). Meta-analysis was not possible due to the low number of total cases (13 children).

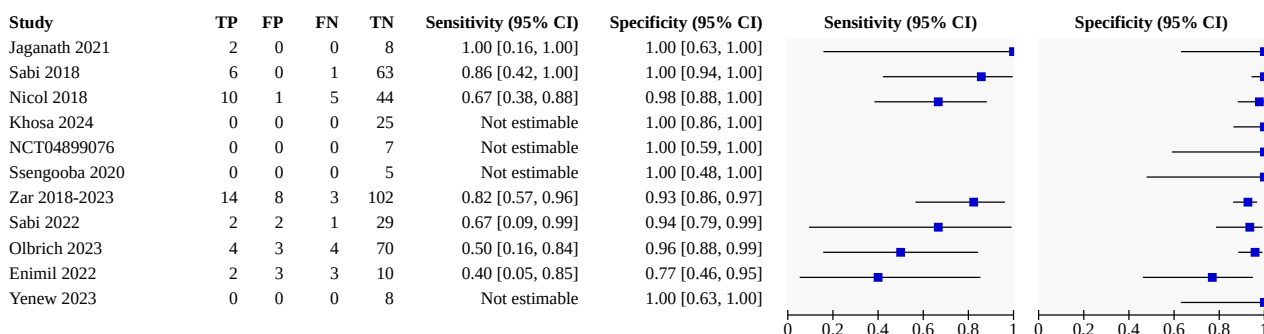
Xpert Ultra accuracy by HIV status

Few studies assessed Xpert Ultra accuracy for pulmonary tuberculosis by specimen type and HIV status. Data were insufficient to perform a meta-analysis for gastric aspirate, nasopharyngeal aspirate, and stool from children living with HIV. [Figure 8](#) presents sensitivity and specificity estimates for individual studies, while [Table 5](#) presents summary estimates. We have described the analyses for each index test against culture below.

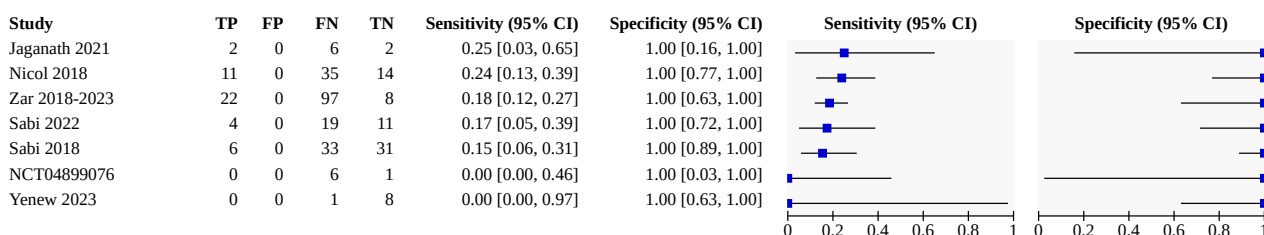
Figure 8. Forest plots of Xpert Ultra sensitivity and specificity for pulmonary tuberculosis by specimen type, HIV status, and reference standard. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

FN: false negative; FP: false positive; TN: true negative; TP: true positive. For stool specimens, microbiological reference standard is used because Xpert on sputum specimens was included in the reference standard.

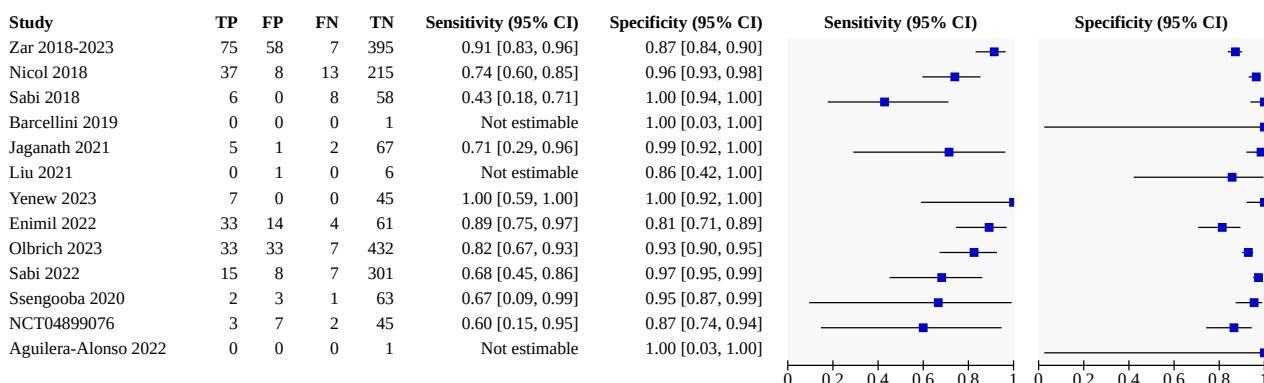
Xpert Ultra, sputum, HIV-positive, 0–9 years, culture



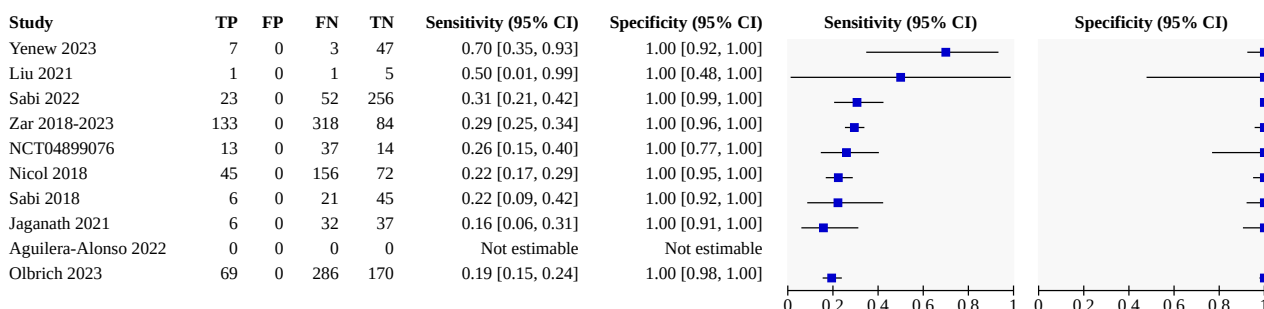
Xpert Ultra, sputum, HIV-positive, 0–9 years, composite reference standard



Xpert Ultra, sputum, HIV-negative, 0–9 years, culture



Xpert Ultra, sputum, HIV-negative, 0–9 years, composite reference standard



Xpert Ultra, gastric aspirate, HIV positive, 0–9 years, culture

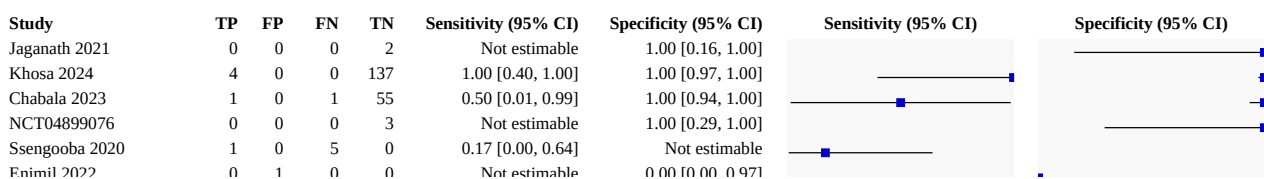


Figure 8. (Continued)

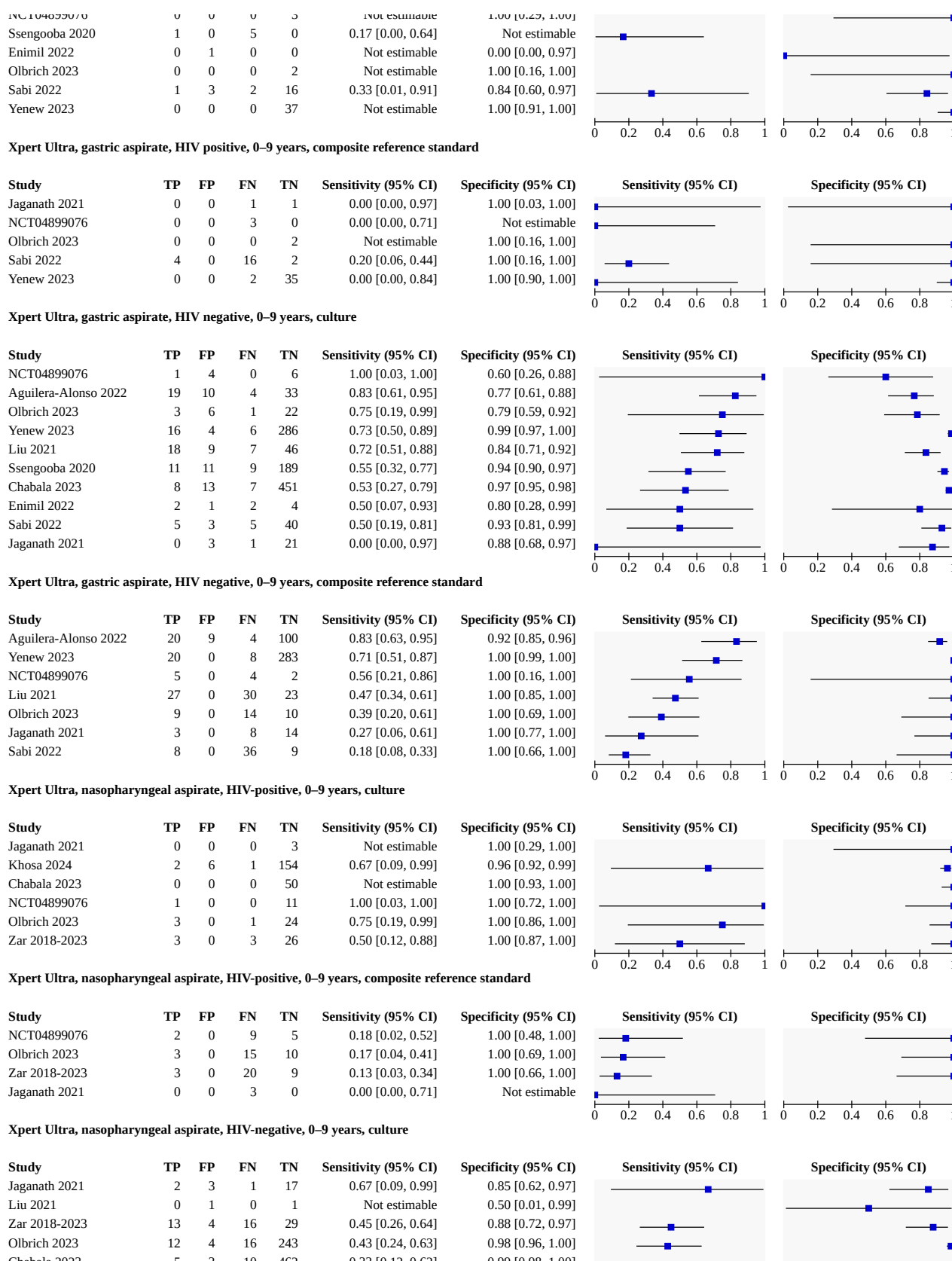
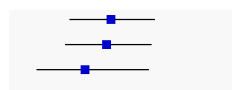
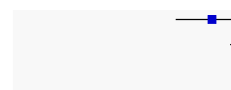

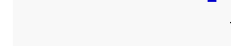

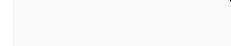
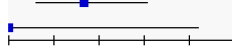
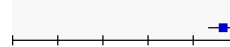
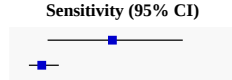

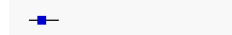
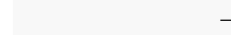
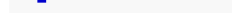
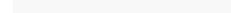


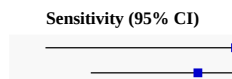
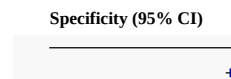



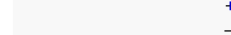

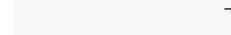

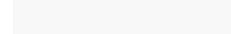

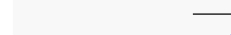
Figure 8. (Continued)

| | | | | | | | | |
|---------------|----|---|----|-----|-------------------|-------------------|--|---|
| Zar 2018-2023 | 13 | 4 | 16 | 29 | 0.45 [0.26, 0.64] | 0.88 [0.72, 0.97] |  |  |
| Olbrich 2023 | 12 | 4 | 16 | 243 | 0.43 [0.24, 0.63] | 0.98 [0.96, 1.00] |  |  |
| Chabala 2023 | 5 | 3 | 10 | 462 | 0.33 [0.12, 0.62] | 0.99 [0.98, 1.00] |  |  |
| NCT04899076 | 0 | 7 | 2 | 97 | 0.00 [0.00, 0.84] | 0.93 [0.87, 0.97] |  |  |

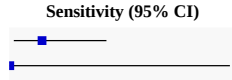
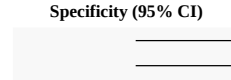
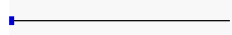
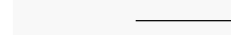
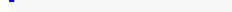
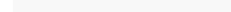
Xpert Ultra, nasopharyngeal aspirate, HIV-negative, 0–9 years, composite reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|-----|----|----------------------|----------------------|--|---|
| Jaganath 2021 | 5 | 0 | 6 | 12 | 0.45 [0.17, 0.77] | 1.00 [0.74, 1.00] |  |  |
| Zar 2018-2023 | 17 | 0 | 103 | 42 | 0.14 [0.08, 0.22] | 1.00 [0.92, 1.00] |  |  |
| NCT04899076 | 10 | 0 | 69 | 37 | 0.13 [0.06, 0.22] | 1.00 [0.91, 1.00] |  |  |

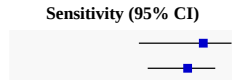

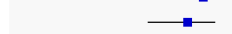
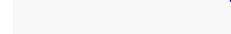
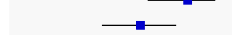
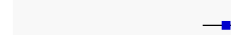

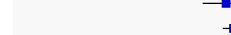

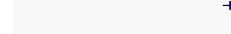

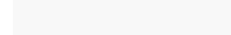
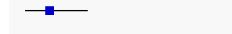
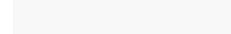
Xpert Ultra, stool, HIV-positive, 0–9 years, microbiological reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|--|---|
| Babo 2023 | 2 | 0 | 0 | 2 | 1.00 [0.16, 1.00] | 1.00 [0.16, 1.00] |  |  |
| Khosa 2024 | 5 | 4 | 1 | 163 | 0.83 [0.36, 1.00] | 0.98 [0.94, 0.99] |  |  |
| de Haas 2022 | 9 | 0 | 2 | 54 | 0.82 [0.48, 0.98] | 1.00 [0.93, 1.00] |  |  |
| Chabala 2023 | 1 | 0 | 1 | 107 | 0.50 [0.01, 0.99] | 1.00 [0.97, 1.00] |  |  |
| NCT04899076 | 2 | 0 | 2 | 16 | 0.50 [0.07, 0.93] | 1.00 [0.79, 1.00] |  |  |
| Yenew 2023 | 0 | 1 | 0 | 46 | Not estimable | 0.98 [0.89, 1.00] |  |  |

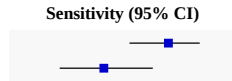


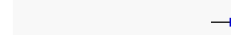

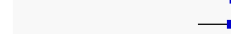

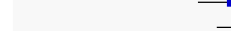
Xpert Ultra, stool, HIV-positive, 0–9 years, composite reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|----|----------------------|----------------------|--|---|
| NCT04899076 | 2 | 0 | 12 | 6 | 0.14 [0.02, 0.43] | 1.00 [0.54, 1.00] |  |  |
| de Haas 2022 | 0 | 0 | 1 | 6 | 0.00 [0.00, 0.97] | 1.00 [0.54, 1.00] |  |  |
| Yenew 2023 | 0 | 1 | 3 | 41 | 0.00 [0.00, 0.71] | 0.98 [0.87, 1.00] |  |  |

Xpert Ultra, stool, HIV-negative, 0–9 years, microbiological reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|--|---|
| Babo 2023 | 12 | 4 | 2 | 171 | 0.86 [0.57, 0.98] | 0.98 [0.94, 0.99] |  |  |
| Yenew 2023 | 26 | 0 | 7 | 335 | 0.79 [0.61, 0.91] | 1.00 [0.99, 1.00] |  |  |
| Liu 2021 | 22 | 3 | 16 | 48 | 0.58 [0.41, 0.74] | 0.94 [0.84, 0.99] |  |  |
| Lounnas 2025 | 1 | 3 | 1 | 114 | 0.50 [0.01, 0.99] | 0.97 [0.93, 0.99] |  |  |
| Chabala 2023 | 11 | 1 | 11 | 921 | 0.50 [0.28, 0.72] | 1.00 [0.99, 1.00] |  |  |
| NCT04899076 | 6 | 0 | 28 | 113 | 0.18 [0.07, 0.35] | 1.00 [0.97, 1.00] |  |  |
| de Haas 2022 | 0 | 0 | 0 | 7 | Not estimable | 1.00 [0.59, 1.00] |  |  |

Xpert Ultra, stool, HIV-negative, 0–9 years, composite reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|--|---|
| Yenew 2023 | 26 | 0 | 11 | 314 | 0.70 [0.53, 0.84] | 1.00 [0.99, 1.00] |  |  |
| de Haas 2022 | 10 | 1 | 14 | 41 | 0.42 [0.22, 0.63] | 0.98 [0.87, 1.00] |  |  |
| Liu 2021 | 24 | 1 | 37 | 27 | 0.39 [0.27, 0.53] | 0.96 [0.82, 1.00] |  |  |
| NCT04899076 | 6 | 0 | 94 | 35 | 0.06 [0.02, 0.13] | 1.00 [0.90, 1.00] |  |  |

Sputum specimens, children living with HIV

Eleven studies (445 children) evaluated Xpert Ultra in sputum against culture in HIV-positive children aged birth to nine years (Enimil 2022; Jaganath 2021; Khosa 2024; NCT04899076; Nicol 2018; Olbrich 2023; Sabi 2018; Sabi 2022; Ssengooba 2020; Yenew 2023; Zar 2018-2023). Four studies contributed no data to the meta-analysis because sensitivity was not estimable (Khosa 2024; NCT04899076; Ssengooba 2020; Yenew 2023). In the remaining seven studies (400 children), Xpert Ultra summary sensitivity was 70.4% (95% CI 56.0% to 81.7%), and summary specificity was 95.6% (95% CI 89.9% to 98.2%).

Sputum specimens, HIV negative

Thirteen studies (2090 children) evaluated Xpert Ultra in sputum against culture in HIV-negative children aged birth to nine years

(Aguilera-Alonso 2022; Barcellini 2019; Enimil 2022; Jaganath 2021; Liu 2021; NCT04899076; Nicol 2018; Olbrich 2023; Sabi 2018; Sabi 2022; Ssengooba 2020; Yenew 2023; Zar 2018-2023). Two studies contributed no data to the meta-analysis because sensitivity was not estimable (Barcellini 2019; Liu 2021). In the remaining 10 studies (2081 children), Xpert Ultra summary sensitivity was 78.3% (95% CI 67.8% to 86.1%), and summary specificity was 95.3% (95% CI 91.1% to 97.6%).

Gastric aspirate specimens, HIV negative

Ten studies (1287 children) evaluated Xpert Ultra in gastric aspirate against culture in HIV-negative children aged birth to nine years (Aguilera-Alonso 2022; Chabala 2023; Enimil 2022; Jaganath 2021; Liu 2021; NCT04899076; Olbrich 2023; Sabi 2022; Ssengooba 2020; Yenew 2023). Xpert Ultra summary sensitivity was 67.8% (95% CI

58.0% to 76.3%), and summary specificity was 90.7% (95% CI 82.5% to 95.2%).

Stool specimens, HIV negative

Seven studies (1863 children) evaluated Xpert Ultra in stool against an MRS in HIV-negative children aged birth to nine years (Babo 2023; Chabala 2023; de Haas 2022; Liu 2021; Lounnas 2025; NCT04899076; Yenew 2023). One study contributed no data to the meta-analysis because sensitivity was not estimable (Liu 2021). Xpert Ultra summary sensitivity was 58.6% (95% CI 35.5% to 78.5%), and summary specificity was 99.5% (95% CI 96.9% to 99.9%).

Nasopharyngeal aspirate specimens, HIV negative

Five studies (699 children) evaluated Xpert Ultra in nasopharyngeal aspirate against culture in HIV-negative children aged birth to nine

years (Chabala 2023; Jaganath 2021; NCT04899076; Olbrich 2023; Zar 2018-2023). One study contributed no data to the meta-analysis because sensitivity was not estimable (Jaganath 2021). Xpert Ultra summary sensitivity was 64.2% (95% CI 24.1% to 91.0%), and summary specificity was 76.9% (95% CI 32.6% to 95.8%).

Xpert Ultra accuracy in children with other comorbid conditions

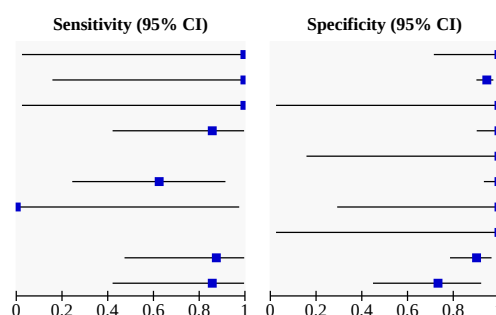
Few studies determined Xpert Ultra accuracy for pulmonary tuberculosis by specimen type in children with severe malnutrition. Figure 9 presents sensitivity and specificity estimates for individual studies, while Table 5 presents summary sensitivity and specificity. There was insufficient data to include nasopharyngeal aspirates in the meta-analysis. We have described the analyses for sputum, gastric aspirate, and stool specimens below.

Figure 9. Forest plots of Xpert Ultra sensitivity and specificity for pulmonary tuberculosis by specimen type and comorbidity, all with microbiological reference standard. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

FN: false negative; FP: false positive; TN: true negative; TP: true positive. For stool specimens, microbiological reference standard is used because Xpert on sputum specimens was included in the reference standard.

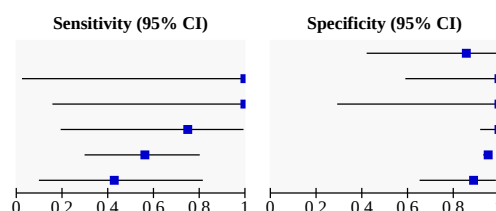
Xpert Ultra, sputum, severe malnutrition, 0–9 years, culture

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------------|----|----|----|-----|----------------------|----------------------|
| Jaganath 2021 | 1 | 0 | 0 | 11 | 1.00 [0.03, 1.00] | 1.00 [0.72, 1.00] |
| Kabir 2020 | 2 | 9 | 0 | 160 | 1.00 [0.16, 1.00] | 0.95 [0.90, 0.98] |
| Yenew 2023 | 1 | 0 | 0 | 1 | 1.00 [0.03, 1.00] | 1.00 [0.03, 1.00] |
| Nicol 2018 | 6 | 0 | 1 | 36 | 0.86 [0.42, 1.00] | 1.00 [0.90, 1.00] |
| NCT04899076 | 0 | 0 | 0 | 2 | Not estimable | 1.00 [0.16, 1.00] |
| Sabi 2022 | 5 | 0 | 3 | 54 | 0.63 [0.24, 0.91] | 1.00 [0.93, 1.00] |
| Ssengooba 2020 | 0 | 0 | 1 | 3 | 0.00 [0.00, 0.97] | 1.00 [0.29, 1.00] |
| Aguilera-Alonso 2022 | 0 | 0 | 0 | 1 | Not estimable | 1.00 [0.03, 1.00] |
| Olbrich 2023 | 7 | 5 | 1 | 46 | 0.88 [0.47, 1.00] | 0.90 [0.79, 0.97] |
| Enimil 2022 | 6 | 4 | 1 | 11 | 0.86 [0.42, 1.00] | 0.73 [0.45, 0.92] |



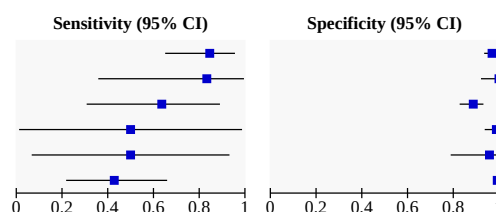
Xpert Ultra, gastric aspirate, severe malnutrition, 0–9 years, culture

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------|----|----|----|-----|----------------------|----------------------|
| Jaganath 2021 | 0 | 1 | 0 | 6 | Not estimable | 0.86 [0.42, 1.00] |
| Ssengooba 2020 | 1 | 0 | 0 | 7 | 1.00 [0.03, 1.00] | 1.00 [0.59, 1.00] |
| Olbrich 2023 | 2 | 0 | 0 | 3 | 1.00 [0.16, 1.00] | 1.00 [0.29, 1.00] |
| Yenew 2023 | 3 | 0 | 1 | 43 | 0.75 [0.19, 0.99] | 1.00 [0.92, 1.00] |
| Chabala 2023 | 9 | 25 | 7 | 504 | 0.56 [0.30, 0.80] | 0.95 [0.93, 0.97] |
| Sabi 2022 | 3 | 2 | 4 | 16 | 0.43 [0.10, 0.82] | 0.89 [0.65, 0.99] |



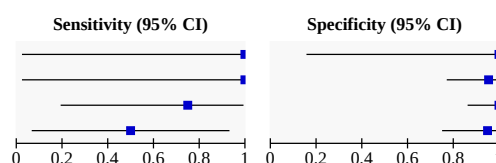
Xpert Ultra, stool, severe malnutrition, 0–9 years, microbiological reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|----|----|----|-----|----------------------|----------------------|
| de Haas 2022 | 22 | 6 | 4 | 192 | 0.85 [0.65, 0.96] | 0.97 [0.94, 0.99] |
| Yenew 2023 | 5 | 0 | 1 | 45 | 0.83 [0.36, 1.00] | 1.00 [0.92, 1.00] |
| Kabir 2020 | 7 | 18 | 4 | 142 | 0.64 [0.31, 0.89] | 0.89 [0.83, 0.93] |
| Khosa 2024 | 1 | 1 | 1 | 86 | 0.50 [0.01, 0.99] | 0.99 [0.94, 1.00] |
| NCT04899076 | 2 | 1 | 2 | 23 | 0.50 [0.07, 0.93] | 0.96 [0.79, 1.00] |
| Chabala 2023 | 9 | 4 | 12 | 518 | 0.43 [0.22, 0.66] | 0.99 [0.98, 1.00] |



Xpert Ultra, nasopharyngeal aspirate, severe malnutrition, 0–9 years, culture

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|----|----------------------|----------------------|
| Jaganath 2021 | 1 | 0 | 0 | 2 | 1.00 [0.03, 1.00] | 1.00 [0.16, 1.00] |
| NCT04899076 | 1 | 1 | 0 | 21 | 1.00 [0.03, 1.00] | 0.95 [0.77, 1.00] |
| Olbrich 2023 | 3 | 0 | 1 | 25 | 0.75 [0.19, 0.99] | 1.00 [0.86, 1.00] |
| Zar 2018-2023 | 2 | 1 | 2 | 19 | 0.50 [0.07, 0.93] | 0.95 [0.75, 1.00] |



Sputum specimens, severe malnutrition

Ten studies (378 children) evaluated Xpert Ultra in sputum against an MRS in children with severe malnutrition (Aguilera-Alonso 2022; Enimil 2022; Jaganath 2021; Kabir 2020; NCT04899076 Nicol 2018; Olbrich 2023; Sabi 2022; Ssengooba 2020; Yenew 2023). Two studies contributed no data to the meta-analysis because sensitivity was not estimable (Aguilera-Alonso 2022; NCT04899076). In the remaining eight studies, Xpert Ultra summary sensitivity was 80.4% (95% CI 62.2% to 91.1%), and summary specificity was 97.2% (95% CI 84.6% to 99.6%).

Gastric aspirate specimens, severe malnutrition

Six studies (637 children) evaluated Xpert Ultra in gastric aspirate specimens against culture in children with severe malnutrition (Chabala 2023; Jaganath 2021; Olbrich 2023; Sabi 2022; Ssengooba 2020; Yenew 2023). One study contributed no data to the meta-analysis (Jaganath 2021). Xpert Ultra summary sensitivity was 60.0% (95% CI 41.9% to 75.7%), and summary specificity was 95.5% (95% CI 93.5% to 96.9%).

Stool specimens, severe malnutrition

Seven studies (1123 children) evaluated Xpert Ultra in stool against culture in children with severe malnutrition (Chabala 2023; de Haas 2022; Kabir 2020; Khosa 2024; Lounnas 2025; NCT04899076; Yenew 2023). All studies were included in the meta-analysis. Xpert Ultra summary sensitivity was 63.8% (95% CI 41.0% to 81.7%), and summary specificity was 97.6% (95% CI 94.1% to 99.0%).

Sensitivity analyses

We excluded studies with an unclear or high risk of bias from analyses of sputum (7 studies), gastric aspirate (6 studies), nasopharyngeal aspirate (5 studies), and stool specimens (4 studies), as shown in [Supplementary material 10](#). In a second sensitivity analysis, we excluded unpublished studies from analyses of sputum (8 studies), gastric aspirate (7 studies), and stool specimens (5 studies), as shown in [Supplementary material 11](#). The results of both sensitivity analyses were consistent with the primary analyses ([Table 3](#)).

Xpert Ultra trace results

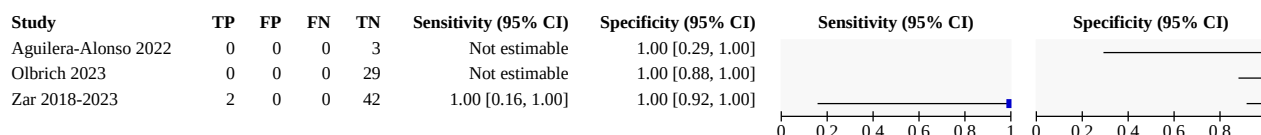
Of the 23 included studies, 18 (78%) reported the number of Xpert Ultra trace results. In these 18 studies, the proportion of trace results among total Xpert Ultra-positive results ranged from 0% to 67% in studies evaluating sputum, 0% to 67% in studies evaluating gastric aspirate, 0% to 40% in studies evaluating nasopharyngeal aspirate, and 0% to 80% in studies evaluating stool ([Table 2](#)).

Detection of rifampicin resistance

Three studies (76 children) evaluated Xpert Ultra for rifampicin resistance from sputum specimens (Aguilera-Alonso 2022; Olbrich 2023; Zar 2018-2023). Only two children (from a single study) had rifampicin resistance, and the sensitivity was 100% (Zar 2018-2023). Specificities were 100% in all three studies ([Figure 10](#)).

Figure 10. Forest plot of Xpert Ultra sensitivity and specificity for rifampicin resistance. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

TP: true positive; FP: false positive; FN: false negative; TN: true negative.



Detection of extrapulmonary tuberculosis

Meta-analysis was not possible for each form of extrapulmonary tuberculosis described below due to sparse data. We did not analyse tuberculous meningitis and lymph node tuberculosis together because they are different disease processes.

Xpert Ultra in cerebrospinal fluid specimens

Culture reference standard

Three studies (215 children) evaluated Xpert Ultra in CSF for diagnosis of tuberculous meningitis against an MRS in children (Olbrich 2023; Pradhan 2022; Zar 2018-2023). Study sensitivities ranged from 67% to 100% and specificities from 91% to 100% ([Figure 11](#)).

Figure 11. Forest plot of Xpert Ultra sensitivity and specificity for diagnosis of extrapulmonary tuberculosis in children. The squares represent the sensitivity and specificity of each study, the black lines their confidence intervals (CIs).

CSF: cerebrospinal fluid; EPTB: extrapulmonary tuberculosis; FP: false positive; FN: false negative; TN: true negative; TP: true positive.

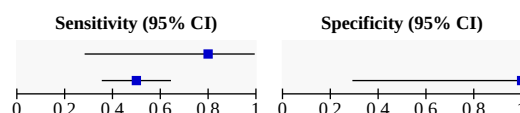
Xpert Ultra, EPTB, lymph node, 0-9 years, culture

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|----|----------------------|----------------------|
| Zar 2018-2023 | 19 | 6 | 0 | 28 | 1.00 [0.82, 1.00] | 0.82 [0.65, 0.93] |
| Aurilio 2022 | 2 | 2 | 0 | 1 | 1.00 [0.16, 1.00] | 0.33 [0.01, 0.91] |



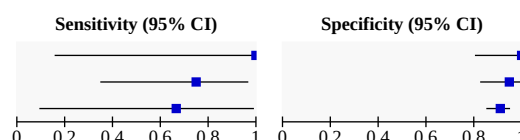
Xpert Ultra, EPTB, lymph node, 0-9 years, composite reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|----|----------------------|----------------------|
| Aurilio 2022 | 4 | 0 | 1 | 0 | 0.80 [0.28, 0.99] | Not estimable |
| Zar 2018-2023 | 25 | 0 | 25 | 3 | 0.50 [0.36, 0.64] | 1.00 [0.29, 1.00] |



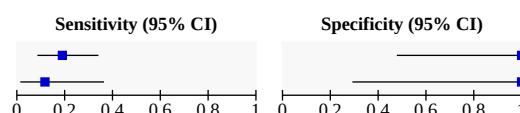
Xpert Ultra, EPTB, CSF, 0-9 years, culture

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|-----|----------------------|----------------------|
| Olbrich 2023 | 2 | 0 | 0 | 17 | 1.00 [0.16, 1.00] | 1.00 [0.80, 1.00] |
| Zar 2018-2023 | 6 | 2 | 2 | 37 | 0.75 [0.35, 0.97] | 0.95 [0.83, 0.99] |
| Pradhan 2022 | 2 | 13 | 1 | 133 | 0.67 [0.09, 0.99] | 0.91 [0.85, 0.95] |



Xpert Ultra, EPTB, CSF, 0-9 years, composite reference standard

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|----|----|----|----|----------------------|----------------------|
| Zar 2018-2023 | 8 | 0 | 34 | 5 | 0.19 [0.09, 0.34] | 1.00 [0.48, 1.00] |
| Olbrich 2023 | 2 | 0 | 15 | 3 | 0.12 [0.01, 0.36] | 1.00 [0.29, 1.00] |



Composite reference standard

Two studies (67 children) evaluated Xpert Ultra in CSF for diagnosis of tuberculous meningitis against a CRS in children (Olbrich 2023; Zar 2018-2023). Sensitivities were 12% and 19%, and specificity was 100% in both studies (Figure 11).

Xpert Ultra in lymph node tissue and aspirates

Culture reference standard

Two studies (58 children) evaluated Xpert Ultra in lymph node tissue and aspirates for diagnosis of lymph node tuberculosis against an MRS in children (Aurilio 2022; Zar 2018-2023). Xpert Ultra had a sensitivity of 100% in both studies, and the specificities were 33% and 82% (Figure 11).

Composite reference standard

Two studies (58 children) evaluated Xpert Ultra in lymph node tissue and aspirates for diagnosis of lymph node tuberculosis against a CRS in children (Aurilio 2022; Zar 2018-2023). The sensitivities were 50% and 80%. Zar 2018-2023 showed a specificity of 100%, and the specificity was not estimable in Aurilio 2022 (Figure 11).

Non-determinate index test results

Non-determinate results for detection of pulmonary tuberculosis

The percentage of non-determinate Xpert Ultra results ranged from 0% to 11% in sputum and from under 1% to 10.8% in stool. Non-determinate results were not reported or could not be disaggregated from other specimen types for Xpert Ultra tests

performed in gastric and nasopharyngeal aspirates. Because only a few non-determinate Xpert Ultra results were reported, the findings are summarized descriptively in Table 2.

Indeterminate results for detection of rifampicin resistance

Only one study had indeterminate results (5 in total) for rifampicin resistance (Olbrich 2023).

DISCUSSION

Summary of main results

This systematic review update summarizes the current literature on the diagnostic accuracy of Xpert Ultra for pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance in children. We identified nine new studies. The main results from the review are summarized in Table 3, Summary of findings 1, and Summary of findings 2.

Xpert Ultra in different types of specimens

Overall, this review adds to the existing body of evidence on the diagnostic accuracy of Xpert Ultra 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. These findings provide new evidence to shape the development of global practice guidelines for the diagnosis of tuberculosis in children.

The diagnostic accuracy of Xpert Ultra in sputum was similar to that presented in the prior review; therefore, our findings may not change current recommendations for these samples

[23]. Compared with the previous version of this review [5], the sensitivity and specificity for nasopharyngeal aspirate and gastric aspirate specimens had tighter CIs, and the point estimate of the sensitivity for Xpert Ultra in stool was higher (68.0%, 95% CI 50.3% to 81.7%; compared with 56.1%, 95% CI 39.1% to 71.7% in the 2022 update)

Against a composite reference standard, we found that Xpert Ultra had a sensitivity that ranged from 12.7% (nasopharyngeal aspirate) to 48.8% (gastric aspirate) and a specificity of greater than 98.7% when considering all specimens.

Xpert Ultra trace results were common (0%–67% of results from sputum, 0%–40% in nasopharyngeal aspirate, 0%–57% in gastric aspirate, and 0%–80% in stool), with the proportion reported in 18/23 studies (Table 2). Existing guidance in children suggests that trace results should be treated as true-positive results [78]; the test remained highly specific despite the high proportion of trace results.

We found the point estimate of the sensitivity of stool Xpert Ultra to be slightly lower at 68.0% (95% CI 50.3% to 81.7%) than that of sputum Xpert Ultra at 75.3% (95% CI 68.9% to 80.8%); sensitivity was statistically similar. Sensitivity was also similar to gastric aspirate Xpert Ultra at 69.6% (95% CI 60.3% to 77.6%). Stool remains a promising specimen for diagnosis because, unlike sputum or gastric aspirates, its collection is non-invasive and can occur in a range of settings, including at the peripheral levels of the healthcare system. Nasopharyngeal aspiration has similar advantages, despite a lower sensitivity. Stool's greatest benefit may be seen in children younger than five years of age owing to the challenges of collecting specimens through sputum induction and gastric aspiration in this population. The sensitivity of stool was 71.6% (95% CI 45.3% to 88.5%) in children aged younger than one year and 74.6% (95% CI 63.1% to 83.4%) in children aged one to four years, suggesting the performance is comparable in younger children. Since the previous review, processing methods for stool have become more standardized, with most studies using the SOS procedure [79]. This may have contributed to the improved sensitivity of stool in this update compared with the previous version.

Subgroup analyses

Xpert Ultra performed similarly well in children with HIV and without HIV. The sensitivity of Xpert Ultra in sputum in children aged birth to nine years living with HIV was 70.4% (95% CI 56.0% to 81.7%), compared with 78.3% (95% CI 67.8% to 86.1%) in HIV-negative children.

In children with severe malnutrition, the sensitivity of Xpert Ultra was 80.4% (95% CI 62.2% to 91.1%) in sputum, 60.0% (95% CI 41.9% to 75.7%) in gastric aspirates, and 63.8% (95% CI 41.0% to 81.7%) in stool.

There was no notable decrease in the sensitivity of Xpert Ultra in children younger than five years of age (versus in children of all ages) in sputum, gastric aspirates, or stool.

Strengths and weaknesses of the review

Completeness of evidence

The data set resulted from comprehensively searching numerous databases, including non-English studies, handsearching

references of included studies, and contacting study authors for additional evidence. We included all identified 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 study authors, including the WHO public call for data. Another limitation is that the search was conducted on 4 October 2023. To keep this updated review aligned with WHO policy guidance, we did not update the literature search. However, in July 2025, we checked if included studies with unpublished data had since been published. We are confident about the comprehensiveness of this review, as we identified no additional unpublished studies through the search or the WHO call for data. We searched for studies of extrapulmonary tuberculosis, but found limited data beyond tuberculous meningitis and lymph node tuberculosis. The review does not include an evaluation of the accuracy of Xpert Ultra in less common forms of tuberculosis in children.

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: a microbiological reference standard (MRS, culture) and a composite reference standard (CRS). Although culture is generally considered the best available MRS, it is not a perfect reference standard in this case owing to the paucibacillary nature of tuberculosis in children. Some studies performed only one culture and others more than one culture to verify tuberculosis. We considered multiple cultures represented a higher-quality reference standard. For technical reasons, we included cultures performed on sputum when evaluating nasopharyngeal aspirates and Xpert Ultra, or culture on sputum or gastric aspirates when evaluating stool (Reference standards). The accuracy of CRS is also variable and limited, but accounts for the paucibacillary nature of tuberculosis in children, which is not taken into account when culture positivity is the reference standard for comparison. For all specimen types, Xpert Ultra sensitivity was lower and specificity similar against a CRS compared with an MRS. 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 CRS. Therefore, clinical characteristics and component tests in the CRS differed across studies, and these differences, as well as incorporation bias due to the inclusion of the MRS into the decision to initiate treatment, may have contributed to variation in accuracy estimates.

Quality assessment and 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. When data were unclear, or when we needed additional information, we corresponded with all primary study authors. Although the methodological quality of the studies was good, for some analyses by age group and comorbidity, the numbers of studies and children enrolled were small, limiting our ability to draw definitive conclusions.

Comparison with other systematic reviews

We are aware of four previously published systematic reviews that estimated the diagnostic accuracy of Xpert Ultra for pulmonary tuberculosis and rifampicin resistance in children [80, 81, 82, 83].

In a 2022 systematic review and meta-analysis by Signorino and colleagues evaluating the diagnostic accuracy of Xpert Ultra for childhood tuberculosis, Xpert Ultra accuracy results were: summary sensitivity 74% (95% CI 66% to 81%) and specificity 97% (95% CI 95% to 98%) in sputum; summary sensitivity 87% (95% CI 76% to 94%) and specificity 85% (95% CI 81% to 89%) in gastric aspirate; summary sensitivity 73% (95% CI 59% to 85%) and specificity 87% (95% CI 84% to 90%) in stool; and summary sensitivity 46% (95% CI 29% to 63%) and specificity 97% (95% CI 94% to 99%) in nasopharyngeal aspirates [80]. These results were similar to ours except for stool and gastric aspirate, which showed higher sensitivity than in our review [80]. For the accuracy estimates in gastric specimens, Signorino and colleagues included only two studies (Parigi 2021; Sun 2020 [84]), whereas we included Parigi 2021 plus another 11 studies, but excluded Sun 2020 [80]. The accuracy estimates for Parigi 2021 were similar in both reviews. For stool specimens, Signorino and colleagues included only two studies (Kabir 2020; Liu 2021), whereas we included these two plus another eight studies [80]. The sensitivity estimates for Kabir 2020 and Liu 2021 were higher in the review by Signorino and colleagues than in our review [80]; this was likely attributable to the different reference standard for stool. Signorino and colleagues used culture on a respiratory specimen as the reference standard for stool, while we used either culture or Xpert Ultra on a respiratory specimen [80]. This difference in reference standard likely also contributed to the lower specificity in the review by Signorino and colleagues [80]. In a 2024 systematic review and meta-analysis by Carratalà-Castro evaluating the diagnostic accuracy of Xpert Ultra on stool for childhood tuberculosis, Xpert Ultra accuracy results were: summary sensitivity 80% (95% CI 62% to 90%) compared to respiratory specimen culture and 73% (95% CI 63% to 81%) compared to any bacteriologic confirmation on a respiratory specimen [83]. The accuracy estimates were similar to our review, with overlapping CIs, but the point estimates may have been slightly higher due to the inclusion of children up to 15 years of age and case-control study designs [83].

A 2020 preliminary systematic review and meta-analysis by Zhang and colleagues evaluating the diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculosis disease included only two studies in children, both focused on sputum specimens [81].

Another review compared the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for detection of pulmonary tuberculosis and rifampicin resistance in adults [82]. It included five studies with 930 participants in total (240 with rifampicin resistance). For detection of rifampicin resistance, Xpert Ultra summary sensitivity was 94.9% (95% credible interval 88.9% to 97.9%), and specificity was 99.1% (95% credible interval 97.7% to 99.8%)

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 three studies (21%) of high concern because children were evaluated exclusively as inpatients in

tertiary care centres. Studies that take place in referral settings may include children whose condition is more advanced or more difficult to diagnose than children seen at lower levels of the health system. With respect to the index test and the reference standard domains, we considered most studies of low applicability concern. Several were unclear because the specimen type used for the reference standard was unclear.

AUTHORS' CONCLUSIONS

Implications for practice

Xpert Ultra sensitivity (defined by culture) for pulmonary tuberculosis was variable, but had largely overlapping confidence intervals across different specimen types, including sputum, gastric aspirate, stool, and nasopharyngeal aspirate. The highest sensitivity point estimate was seen in sputum, followed by gastric aspirate and stool, and the lowest in nasopharyngeal aspirate. Xpert Ultra specificity was high in all specimen types. However, the evidence base is still limited, and findings may be imprecise and vary by study setting. Additional data are needed on the differential performance of Xpert Ultra by specimen type to guide recommendations for diagnostic algorithms in children. Considerations on the best specimen type may depend as much on the equipment and capacity at the health facility where the child is presenting as on the variation of diagnostic accuracy by specimen type. The sensitivity of Xpert Ultra in children aged birth to four years was similar to that in children aged five to nine years and in those aged birth to nine years, in line with our prior findings.

The results for the accuracy of Xpert Ultra for detecting rifampicin resistance were based on very few studies that included only two children with rifampicin resistance. Therefore, findings should be interpreted with caution, and extrapolation from adult data would be reasonable.

Evidence in this review is based mainly on culture, the microbiological reference standard, and we calculated Xpert Ultra accuracy on the assumption that the reference standard is 100% sensitive and specific. Although culture is acceptable, it is an imperfect reference standard for tuberculosis in children. In the absence of a more accurate reference standard, with 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 Ultra result, clinicians will still need to consider tuberculosis treatment in children with a high suspicion of tuberculosis or at high risk of a poor outcome. In our update from the prior review, the percentage of non-determinate results was similar in sputum and stool specimens, likely due to the use of the standardized simple one-step stool processing method.

The evidence from our prior review informed the World Health Organization (WHO) guidelines on the management of tuberculosis in children and adolescents (module 5) [85], and the current review will inform the WHO guidelines on rapid diagnostics for tuberculosis detection (module 3). Specific recommendations from those guidelines, with implications for practice, are presented in Table 1.

Implications for research

There are several areas for which additional research regarding the diagnostic accuracy of molecular tests in children is necessary. There is a need for:

- data to evaluate how Xpert Ultra impacts patient-important outcomes in children, and how Xpert Ultra diagnostic accuracy changes when multiple specimen types are evaluated;
- studies that evaluate the accuracy of Xpert Ultra for detecting extrapulmonary tuberculosis in children. This is particularly relevant given the encouraging results regarding Xpert Ultra performance in cerebrospinal fluid obtained from children [Pradhan 2022];
- more research to identify an improved reference standard that accurately defines tuberculosis in children and is not limited by incorporation bias;
- accurate tests that can be performed by different cadres of healthcare workers at the point of care;
- additional operational and qualitative research 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;
- additional operational research concerning the use of stool as a diagnostic specimen. These studies should address integration into normal diagnostic clinical pathways, definition of laboratory protocols (including processing methods) that successfully balance ease of implementation and diagnostic performance, and the impact of stool testing on patient-important outcomes;
- 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.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD013359.pub4](https://doi.org/10.1002/14651858.CD013359.pub4).

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Analyses

Supplementary material 5 Data package

Supplementary material 6 Data extraction form

Supplementary material 7 Example of 2 × 2 result table

Supplementary material 8 QUADAS-2 review-specific guidance

Supplementary material 9 Methodological quality by specimen and reference standard

Supplementary material 10 Sensitivity analysis – studies at high risk of bias excluded

Supplementary material 11 Sensitivity analysis-unpublished studies excluded

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this review update.

- Sign-off Editor (final editorial decision): Danielle Van Der Windt, School of Medicine, Keele University (DTA); Toby Lasserson, Deputy Editor In Chief, (clinical)
- Managing Editor (provided editorial guidance to authors, edited the article): Ben Ridley, Cochrane Central Editorial Service
- Editorial Assistant (selected peer reviewers, conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Julia Turner, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Beno Huglin Mbeya, Ifakara Health Institute (clinical/content review); Danielle Van Der Windt, School of Medicine, Keele University (methods); Sofia Tsokani, Methods Support Unit, Cochrane CET (statistics); Sophie Robinson, University of Exeter (search). One additional peer reviewer provided clinical peer review but chose not to be publicly acknowledged.

Contributions of authors

AWK, MM, TN, LRI, MKSN, and PA assessed articles for inclusion and extracted data. AWK, MM, and TN resolved disagreements.

AWK, MM, and TN entered data.

AWK, MM, KS, and YT analysed the data and interpreted the analyses. In particular, KS performed statistical analyses.

AWK, MM, KS, and YT reviewed the protocol and co-ordinated the presentation of the findings to a WHO Guideline Development Group.

AWK, MM, TN, and YT drafted the manuscript.

AMM, KRS, LRI, MKSN, LGF, ME, NI, AK, SEV, AB, KV, and TM provided critical comments on the manuscript.

All review authors helped to conceptualize this work, provided input on and approved the final manuscript draft. The author Anne K Detjen, who was involved in previous published versions of this review in 2020 and 2022, is no longer included on the author byline. Some of the content retained in this review reflects her contributions.

Declarations of interest

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

MM has no known conflicts of interest.

KS has no conflict of interest.

TN has no known conflicts of interest.

PA has no known conflicts of interest.

LRI has no known conflicts of interest.

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ME is a Cochrane Infectious Disease Group Editor, and has no known conflicts of interest. ME was not involved in the editorial process for this review.

NI is a WHO staff member in the Global Tuberculosis Programme, which commissioned the 2024 update for tuberculosis molecular diagnostics.

AKo is a WHO staff member in the Global Tuberculosis Programme, which commissioned the 2024 update for tuberculosis molecular diagnostics.

SEV is a Medical Officer at the World Health Organization Global Tuberculosis Programme, which commissioned this review update for the 2022 WHO consolidated guidelines on the management of tuberculosis in children and adolescents.

AB works as a technical officer at the WHO Global Tuberculosis Programme, which commissioned this review update for the 2022 WHO consolidated guidelines on the management of tuberculosis in children and adolescents.

KV is a WHO staff member in the Global Programme on Tuberculosis and Lung Health, which commissioned the 2022 review for the Guideline Development Group meeting on TB in children and adolescents and the 2024 update for the TB diagnostics Guideline Development Group meeting.

TM is a WHO consultant in the Global Programme on Tuberculosis and Lung Health, which commissioned the 2022 review for the Guideline Development Group meeting on TB in children and adolescents and the 2024 update for the TB diagnostics Guideline Development Group meeting.

AMM has conducted prior primary research on tuberculosis diagnostics and has no known conflicts of interest. She has undertaken work as an independent contractor for Janssen Global Services.

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YT is a Cochrane Editorial Board Member and was previously a Cochrane Infectious Diseases Group Editor. She was not involved in the editorial process for this review.

The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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Registration and protocol

The protocol for this review was originally published through Cochrane in 2019. The protocol for this update is a generic protocol that consolidated previously published Cochrane protocols of Xpert Ultra for tuberculosis detection and can be accessed at <https://osf.io/26wg7/>.

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Original review (2020) DOI: 10.1002/14651858.CD013359.pub2

Review update (2022) DOI: 10.1002/14651858.CD013359.pub3

Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included or excluded at the full text screen in the final review; study data, including study information and test data; and consensus risk of bias assessments. Some analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Scripts used to generate analyses outside RevMan in Stata and template data

extraction forms are available from the authors on reasonable request.

What's new

| Date | Event | Description |
|-----------------|--|--|
| 23 October 2025 | New citation required but conclusions have not changed | The conclusions on the diagnostic accuracy of Xpert Ultra in children remain unchanged in this review update. |
| 23 October 2025 | New search has been performed | The search was updated on 4 to 6 October 2023, and additional data on Xpert Ultra was incorporated for all specimen types to update the previous review. Nine new studies were added, bringing the total number of included studies to 23. |

History

Protocol first published: Issue 6, 2019

Review first published: Issue 8, 2020

| Date | Event | Description |
|----------------|--|---|
| 31 August 2022 | New search has been performed | The previous published review version assessed the accuracy of both Xpert MTB/RIF and Xpert Ultra. The authors limited this review update to Xpert Ultra, which has superseded Xpert MTB/RIF. The Xpert MTB/RIF text and analyses are available in the previous published review version. |
| 31 August 2022 | New citation required and conclusions have changed | The date of search was updated to 9 March 2021. The authors included 14 unique studies, integrating 11 new studies since the previous published review version. |

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ADDITIONAL TABLES

Table 1. Current World Health Organization (WHO) diagnostic recommendations in children

[23]^a

In children with signs and symptoms of pulmonary tuberculosis, Xpert Ultra should be used as the initial diagnostic test for tuberculosis and detection of rifampicin resistance in sputum or nasopharyngeal aspirate, rather than smear microscopy/culture and phenotypic drug susceptibility testing (strong recommendation, low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate).

In children with signs and symptoms of tuberculous meningitis, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for tuberculous meningitis rather than smear microscopy/culture (strong recommendation, moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra).

Table 1. Current World Health Organization (WHO) diagnostic recommendations in children *(Continued)*

In children with signs and symptoms of extrapulmonary tuberculosis, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test rather than smear microscopy/culture (conditional recommendation, low certainty of evidence).

In children with presumed pulmonary tuberculosis and an initial Xpert Ultra-negative result, in settings with a pretest probability of 5% or more, WHO recommends a repeat Xpert Ultra test (for a total of two tests). Sputum and nasopharyngeal aspirate specimens may be used (conditional recommendation, very low certainty of evidence for test accuracy).

[85]^b

In children aged below 10 years with signs and symptoms of pulmonary tuberculosis, Xpert MTB/RIF Ultra should be used in gastric aspirate or stool specimens as the initial diagnostic test for tuberculosis and the detection of rifampicin resistance, rather than smear microscopy/culture and phenotypic drug susceptibility testing.

^a The findings from [4] informed development of the guidelines.

^b The findings from this review update will inform the next version of the guidelines.

Table 2. Key characteristics of included studies

| Study | Target condition | Index test | Reference standard | Study design | Sample size | HIV status | Clinical setting | High tuberculosis burden | Type of specimens | Xpert Ultra non-determinate from stool ^a % (number/total) | Xpert Ultra trace ^b % (number) | Funding source |
|----------------------|------------------|-------------|----------------------------------|-----------------------|-------------|--------------|------------------|--------------------------|-------------------|---|---|---|
| Aguilera-Alonso 2022 | PTB | Xpert Ultra | Culture, composite | Prospective cohort | 75 | Negative | Not reported | No | Sputum, GA | Not reported | Sputum: 0% (0); GA: 19.7% (13) | No project-specific funding; Xpert Ultra cartridges provided by Cepheid |
| Aurilio 2022 | EPTB | Xpert Ultra | Culture | Prospective cohort | 23 | Not reported | Not reported | Yes | Extrapulmonary | Not reported | N/A | Brazilian Council for Research and Technological Development |
| Babo 2023 | PTB | Xpert Ultra | Culture ^c | Prospective cohort | 373 | Both | Outpatient | Yes | Stool | 2.4% (9/373); repeat: 0.8% (3/373) | Stool: 1.9% (6) | Sint Antonius Stichting Projects |
| Barcellini 2019 | PTB | Xpert Ultra | Culture | Cross-sectional | 3 | Negative | Outpatient | No | Sputum | Not reported | N/A | EU Health Programme |
| Chibolela 2023 | PTB | Xpert Ultra | Culture | Cross-sectional | 116 | Both | Not reported | No | Stool | Not reported | Stool: 0% (0) | Zambia National TB Programme and Longhorn Vaccines and Diagnostics LLC |
| de Haas 2022 | PTB | Xpert Ultra | Culture ^c , composite | Prospective ("pilot") | 690 | Both | Not reported | Yes | Stool | Among PLHIV initial: 11.6% (37/319); repeat: 3.8% (12/319) Among children initial: | Stool: 4.5% (10) | The Global Fund |

Table 2. Key characteristics of included studies (Continued)

| | | | | | | | | | | | | |
|-----------------------|--------------|------------------|----------------------------|-------------------------|-----|-------------------|---------------------------------------|-----|--|---|---|---|
| | | | | | | | | | | 10.8% (40/370); repeat: 6.2% (23/370) | | |
| Enimil 2022 | PTB | Xpert Ul- tra | Culture | Retrospec- tive | 174 | Both | Not re- ported | Yes | Sputum, GA | Not re- ported | N/A | No project-specif- ic funding |
| Ja- ganath 2021 | PTB | Xpert Ul- tra | Culture, compos- ite | Prospec- tive cohort | 213 | Both | Inpa- tient and outpa- tient | No | Sputum, GA, NPA | Not re- ported | Sputum: 12% (2); GA: 67% (2); NPA: 40% (2) | NHLBI and NICHD |
| Kabir 2020 | PTB | Xpert Ul- tra | Culture, compos- ite | Cross-sec- tional | 447 | Not re- ported | Inpa- tient | Yes | Sputum, stool | < 1% (1/446) | Sputum: 39% (11); stool: 80% (48) | USAID and DFID |
| Liu 2021 | PTB | Xpert Ul- tra | Culture, compos- ite | Prospec- tive cohort | 311 | Negative | Inpa- tient and outpa- tient | Yes | Sputum, GA, NPA, stool | Not re- ported | Sputum: 0%; GA: 30% (8); stool: 38% (16); NPA: 0% | Chinese Nation- al Mega Science and Technology Program on In- fectious Diseases, National Key R&D Program of Chi- na, and National Science Founda- tion of China |
| Olbrich 2023 | PTB, EPTB | Xpert Ul- tra | Culture, compos- ite | Prospec- tive cohort | 975 | Both | Inpa- tient and outpa- tient | Yes | Sputum, GA, NPA, extrapul- monary | Not re- ported | GA: 14.7% (5); sputum: 5.0% (30); NPA: 3.5% (11); CSF: 0% (0); LN: 0% (0) | EDCTP and partnered with Cepheid and Beckman Coulter |
| Khosa 2024 | PTB | Xpert Ul- tra | Culture | Prospec- tive cohort | 277 | Positive | Inpa- tient and outpa- tient | Yes | Sputum, GA, NPA, stool | 4% (5/114) | Sputum: 0% (0); GA: 0% (0); NPA: 2.5% (4); stool: 2.1% (3) | Unitaid |

Table 2. Key characteristics of included studies (Continued)

| | | | | | | | | | | | | |
|-----------------|-------------------|-------------|--------------------|--------------------|-----|----------|--------------------------|-----|------------------------|--------------|--|--|
| Lounnas 2025 | PTB | Xpert Ultra | Culture | Prospective cohort | 111 | Both | Inpatient and outpatient | Yes | Stool | 3% (2/76) | Stool: 40% (2) | Unitaid |
| Chabala 2023 | PTB | Xpert Ultra | Culture | Prospective cohort | 603 | Both | Inpatient | Yes | GA, NPA, stool | 1% (2/237) | GA: 2.2% (12); NPA: 0.4% (2); stool: 1.2% (6) | Unitaid |
| NCT04899078 | PTB | Xpert Ultra | Culture, composite | Prospective cohort | 486 | Both | Inpatient and outpatient | Yes | Sputum, GA, NPA, stool | 10% (42/434) | Sputum: 10% (7); GA: 15% (3); NPA: 5.6% (7); stool: 1.6% (3) | FIND |
| Nicol 2018 | PTB | Xpert Ultra | Culture, composite | Prospective cohort | 367 | Both | Inpatient | Yes | Sputum | 11% (50/453) | Sputum: 21.9% (14) | South Africa MRC and OAR |
| Parigi 2021 | PTB | Xpert Ultra | Culture, composite | Prospective cohort | 67 | Negative | Inpatient | No | GA | Not reported | N/A | Not reported |
| Pradhan 2022 | EPTB (meningitis) | Xpert Ultra | Culture, composite | Prospective cohort | 149 | Both | Inpatient | Yes | CSF | Not reported | N/A | NICHD |
| Sabi 2018 | PTB | Xpert Ultra | Culture, composite | Prospective cohort | 215 | Both | Inpatient and outpatient | Yes | Sputum | 0% (0/215) | N/A | EDCTP and FIND |
| Sabi 2022 | PTB | Xpert Ultra | Culture | Prospective cohort | 547 | Both | Outpatient | Yes | Sputum, GA | Not reported | Sputum: 19% (3) | UK MRC and FIND provided support for Xpert MTB/RIF Ultra cartridges. |
| Ssen-gooba 2020 | PTB | Xpert Ultra | Culture | Prospective Cohort | 398 | Both | Outpatient | Yes | Sputum, GA | Not reported | N/A | Joint Global Health Trials Scheme of DFID, DHSC, UK MRC |

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Table 2. Key characteristics of included studies (Continued)

| | | | | | | | | | | | | |
|------------------|--------------|-------------|-------------------------------------|--------------------|-----|------|-----------------------------|-----|--------------------------------|--|--|--|
| Yenew 2023 | PTB | Xpert Ultra | Culture ^c , composite | Prospective cohort | 898 | Both | Inpatient and outpatient | No | Sputum, GA, stool | Initial: 5.8% (50/862); repeat: 2.8% (24/862) | Sputum: 67% (4); GA: 57% (13) | USAID, Dutch Directorate-General for International Cooperation through WHO |
| Zar 2018-2023 | PTB, EPTB | Xpert Ultra | Culture, composite | Prospective cohort | 773 | Both | Inpatient and outpatient | Yes | Sputum, NPA, extrapulmonary | Not reported | Stool: 1.2% (9); GA: 1.2% (8); sputum: 1.9% (2) | South Africa MRC and OAR |

^a Non-determinate results are Error, Invalid, or No Result.

^b Calculated as percentage of total number of positive tests.

^c For stool, Xpert on respiratory specimens was the reference standard.

DFID: UK Department for International Development; **DHSC:** UK Department of Health and Social Care; **EDCTP:** European and Developing Countries Clinical Trials Partnership; **EPTB:** extrapulmonary tuberculosis; **EU:** European Union; **FIND:** Foundation for Innovative New Diagnostics; **GA:** gastric aspirate; **MRC:** Medical Research Council; **NHLBI:** US National Heart, Lung, and Blood Institute; **NIH:** US National Institutes of Health; **NICHD:** US National Institute of Child Health and Human Development; **NPA:** nasopharyngeal aspirate; **OAR:** NIH Office of AIDS Research; **PTB:** pulmonary tuberculosis; **R&D:** research and development; **USAID:** US Agency for International Development; **WHO:** World Health Organization.

Table 3. Xpert Ultra summary sensitivity and specificity for pulmonary tuberculosis, by type of specimen and reference standard

| Analysis | Reference standard | Studies | Number of children (TB cases) | Summary sensitivity % (95% CI) | Summary specificity % (95% CI) | Positive predictive value % (95% CI) ^a | Negative predictive value % (95% CI) ^a |
|------------------|--------------------|---------|-------------------------------|--------------------------------|------------------------------------|---|---|
| Sputum | Culture | 11 | 2990 (345) | 75.3 (68.9 to 80.8) | 95.9 (92.3 to 97.9) | 67.1 (49.8 to 80.7) | 97.2 (96.4 to 97.9) |
| Sputum | Composite | 10 | 2823 (1626) | 23.5 (20.3 to 27.0) | 100.0 ^b (99.7 to 100.0) | 100.0 (88.0 to 100.0) | 92.2 (91.8 to 92.5) |
| Sputum; CLHIV | Culture | 7 | 400 (57) | 70.4 (56.0 to 81.7) | 95.6 (89.9 to 98.2) | 64.2 (38.0 to 83.4) | 96.7 (94.8 to 98.0) |
| Sputum; CLHIV | Composite | 7 | 317 (242) | 18.6 (14.2 to 24.0) | 100.0 ^b (95.2 to 100.0) | 100.0 (24.7 to 100.0) | 91.7 (90.9 to 92.2) |

Table 3. Xpert Ultra summary sensitivity and specificity for pulmonary tuberculosis, by type of specimen and reference standard (Continued)

| | | | | | | | |
|-------------------------|-----------------|----|------------|---------------------|------------------------------------|-----------------------|---------------------|
| Gastric aspirate | Culture | 12 | 1959 (167) | 69.6 (60.3 to 77.6) | 91.0 (82.5 to 95.6) | 46.2 (27.6 to 66.1) | 96.4 (94.9 to 97.5) |
| Gastric aspirate | Composite | 7 | 1057 (267) | 48.8 (31.4 to 63.7) | 98.7 (97.7 to 99.3) | 81.1 (59.9 to 91.2) | 94.5 (92.8 to 96.1) |
| Stool | Microbiological | 10 | 2885 (255) | 68.0 (50.3 to 81.7) | 98.2 (96.3 to 99.1) | 80.9 (60.4 to 91.3) | 96.5 (94.6 to 98.0) |
| Stool | Composite | 6 | 1778 (510) | 31.4 (17.2 to 50.2) | 99.0 (97.4 to 99.6) | 77.3 (42.3 to 93.4) | 92.8 (91.4 to 94.7) |
| Nasopharyngeal aspirate | Culture | 6 | 1353 (94) | 46.2 (34.9 to 57.9) | 97.5 (95.1 to 98.7) | 67.2 (44.3 to 83.5) | 94.2 (92.9 to 95.5) |
| Nasopharyngeal aspirate | Composite | 4 | 676 (465) | 12.7 (9.2 to 17.3) | 100.0 ^b (98.3 to 100.0) | 100.0 (37.2 to 100.0) | 91.2 (90.7 to 91.6) |

^a Predictive values were determined at a pretest probability of 10%.

^b Meta-analysis using univariate fixed-effect or random-effects logistic regression models is not possible when all studies in a meta-analysis report 100% specificity. Therefore, the summary specificity was calculated by dividing the total number of non-cases by the total number of true negatives.

CI: confidence interval; **CLHIV:** children living with HIV; **TB:** tuberculosis.

Table 4. Xpert Ultra summary sensitivity and specificity for pulmonary tuberculosis, by type of specimen, age group, and reference standard

| Age group | Reference standard | Studies | Number of children (TB cases) | Summary sensitivity % (95% CI) | Summary specificity % (95% CI) | Positive predictive value % (95% CI) ^a | Negative predictive value % (95% CI) ^a |
|-----------------|--------------------|---------|-------------------------------|--------------------------------|------------------------------------|---|---|
| Sputum specimen | | | | | | | |
| < 1 year | Culture | 8 | 635 (67) | 81.7 (67.8 to 90.4) | 96.3 (85.1 to 99.2) | 71.1 (33.5 to 92.4) | 97.9 (96.0 to 98.9) |
| <1 year | Composite | 9 | 620 (363) | 21.8 (16.2 to 28.6) | 100.0 ^b (98.6 to 100.0) | 100.0 (55.9 to 100.0) | 92.0 (91.4 to 92.6) |
| 1–4 years | Culture | 10 | 1420 (154) | 74.6 (63.1 to 83.4) | 95.3 (92.3 to 97.2) | 63.8 (47.6 to 76.6) | 97.1 (95.7 to 98.1) |
| 1–4 years | Composite | 9 | 1339 (812) | 21.8 (18.3 to 25.6) | 100.0 ^b (99.3 to 100.0) | 100.0 (74.5 to 100.0) | 92.0 (91.6 to 92.4) |
| 5–9 years | Culture | 11 | 890 (112) | 81.9 (65.3 to 91.6) | 95.4 (91.6 to 97.6) | 66.6 (46.3 to 80.6) | 97.9 (96.0 to 99.0) |
| 5–9 years | Composite | 9 | 861 (451) | 27.4 (21.2 to 34.6) | 100.0 ^b (99.1 to 100.0) | 100.0 (72.4 to 100.0) | 92.5 (91.9 to 93.2) |

Table 4. Xpert Ultra summary sensitivity and specificity for pulmonary tuberculosis, by type of specimen, age group, and reference standard (Continued)

| | | | | | | | |
|---|-----------|----|------------|----------------------|------------------------------------|-----------------------|---------------------|
| Gastric aspirate specimen | | | | | | | |
| < 1 year | Culture | 10 | 509 (49) | 77.2 (59.3 to 88.7) | 84.4 (66.2 to 93.7) | 35.4 (16.3 to 61.0) | 97.1 (93.6 to 98.7) |
| < 1 year | Composite | 6 | 299 (71) | 78.1 (35.8 to 95.8) | 98.2 (95.4 to 99.3) | 83.2 (46.5 to 94.2) | 97.6 (93.0 to 99.5) |
| 1–4 years | Culture | 9 | 1104 (89) | 72.8 (55.4 to 85.3) | 95.6 (88.8 to 98.4) | 64.9 (35.5 to 85.3) | 96.9 (94.7 to 98.4) |
| 1–4 year | Composite | 7 | 549 (134) | 45.8 (23.5 to 69.9) | 99.0 (97.5 to 99.6) | 84.1 (50.7 to 95.5) | 94.3 (92.0 to 96.7) |
| 5–9 years | Culture | 8 | 266 (28) | 56.8 (38.0 to 73.9) | 93.0 (84.3 to 97.0) | 47.4 (21.2 to 73.4) | 95.1 (92.5 to 97.1) |
| 5–9 years | Composite | 5 | 181 (50) | 33.9 (22.0 to 48.3) | 98.9 (82.7 to 99.9) | 77.0 (12.4 to 98.9) | 93.1 (90.5 to 94.6) |
| Stool specimen | | | | | | | |
| < 1 year | Culture | 8 | 771 (78) | 71.6 (45.3 to 88.5) | 97.0 (93.7 to 98.6) | 72.9 (44.3 to 87.9) | 96.9 (93.9 to 98.7) |
| < 1 year | Composite | 6 | 517 (130) | 44.5 (31.6 to 58.2) | 98.3 (94.4 to 99.5) | 73.9 (38.5 to 92.4) | 94.1 (92.5 to 95.5) |
| 1–4 years | Culture | 7 | 1420 (154) | 57.9% (44.6 to 70.3) | 98.1% (95.3 to 99.3) | 63.8 (47.6 to 76.6) | 97.1 (95.7 to 98.1) |
| 1–4 years | Composite | 5 | 746 (199) | 28.3 (12.0 to 53.3) | 99.3 (97.4 to 99.8) | 81.0 (33.5 to 96.7) | 92.6 (90.9 to 95.1) |
| 5–9 years | Culture | 7 | 651 (59) | 62.9 (39.5 to 81.5) | 98.0 (93.9 to 99.4) | 77.8 (41.7 to 93.5) | 96.0 (93.3 to 98.0) |
| 5–9 years | Composite | 5 | 424 (117) | 38.2 (23.6 to 55.3) | 99.3 (97.4 to 99.8) | 86.7 (50.6 to 97.4) | 93.5 (92.0 to 95.3) |
| Nasopharyngeal aspirate specimen ^c | | | | | | | |
| < 1 year | Composite | 4 | 147 (103) | 14.6 (09.0 to 22.8) | 100.0 ^b (92.0 to 100.0) | 100.0 (11.0 to 100.0) | 91.3 (90.1 to 92.1) |
| 1–4 years | Culture | 5 | 799 (57) | 49.3 (36.2 to 62.5) | 98.7 (96.6 to 99.5) | 81.0 (54.5 to 93.5) | 94.6 (93.2 to 96.0) |
| 1–4 years | Composite | 4 | 446 (310) | 11.0 (06.9 to 17.1) | 100.0 ^b (97.3 to 100.0) | 100.0 (22.4 to 100.0) | 91.0 (90.4 to 91.6) |
| 5–9 years | Composite | 4 | 82 (52) | 19.2 (10.7 to 32.2) | 100.0 ^b (88.4 to 100.0) | 100.0 (09.3 to 100.0) | 91.8 (89.9 to 93.0) |

^a Predictive values were determined at a pretest probability of 10%.

^b Meta-analysis using univariate fixed-effect or random-effects logistic regression models is not possible when all studies in a meta-analysis report 100% specificity. Therefore, the summary specificity was calculated by dividing the total number of non-cases by the total number of true negatives.

^c Meta-analysis was not possible for nasopharyngeal aspirates against a microbiological reference standard for children aged under one year due to sparse data.
CI: confidence interval; **TB:** tuberculosis.

Table 5. Xpert Ultra summary sensitivity and specificity by type of specimen, comorbidity status, and reference standard

| Comorbidity status | Reference standard | Studies | Number of children (TB cases) | Summary sensitivity % (95% CI) | Summary specificity % (95% CI) | Positive predictive value % (95% CI) ^a | Negative predictive value % (95% CI) ^a |
|---------------------------|--------------------|---------|-------------------------------|--------------------------------|------------------------------------|---|---|
| Sputum specimen | | | | | | | |
| CLHIV | Culture | 7 | 400 (57) | 70.4 (56.0 to 81.7) | 95.6 (89.9 to 98.2) | 64.2 (38.0 to 83.4) | 96.7 (94.8 to 98.0) |
| CLHIV | Composite | 7 | 317 (242) | 18.6 (14.2 to 24.0) | 100.0 ^b (95.2 to 100.0) | 100.0 (24.7 to 100.0) | 91.7 (90.9 to 92.2) |
| HIV negative | Culture | 10 | 2081 (267) | 78.3 (67.8 to 86.1) | 95.3 (91.1 to 97.6) | 64.9 (46.0 to 79.7) | 97.5 (96.2 to 98.4) |
| HIV negative | Composite | 9 | 1939 (1209) | 25.3 (21.0 to 30.1) | 100.0 ^b (99.5 to 100.0) | 100.0 (82.2 to 100.0) | 92.3 (91.9 to 92.8) |
| Severe malnutrition | Culture | 8 | 375 (35) | 80.4 (62.2 to 91.1) | 97.2 (84.6 to 99.6) | 76.2 (31.0 to 95.8) | 97.8 (95.3 to 99.0) |
| Severe malnutrition | Composite | 7 | 354 (163) | 23.3 (17.5 to 30.4) | 100.0 ^b (98.1 to 100.0) | 100.0 (50.3 to 100.0) | 92.1 (91.4 to 92.8) |
| Gastric aspirate specimen | | | | | | | |
| HIV negative | Culture | 10 | 1287 (125) | 67.8 (58.0 to 76.3) | 90.7 (82.5 to 95.2) | 44.7 (26.9 to 64.1) | 96.2 (94.6 to 97.3) |
| HIV negative | Composite | 7 | 646 (196) | 48.8 (30.8 to 67.1) | 98.0 (96.2 to 99.0) | 73.0 (47.4 to 87.7) | 94.5 (92.6 to 96.4) |
| Severe malnutrition | Culture | 5 | 630 (30) | 60.0 (41.9 to 75.7) | 95.5 (93.5 to 96.9) | 59.7 (41.8 to 73.0) | 95.6 (93.5 to 97.3) |
| Severe malnutrition | Composite | 4 | 88 (38) | 31.6 (18.9 to 47.8) | 100.0 ^b (92.9 to 100.0) | 100.0 (22.8 to 100.0) | 92.9 (91.2 to 94.5) |
| Stool specimen | | | | | | | |
| HIV negative | MRS | 6 | 1856 (143) | 58.6 (35.5 to 78.5) | 99.5 (96.9 to 99.9) | 92.6 (56.3 to 99.0) | 95.6 (93.1 to 97.7) |
| HIV negative | Composite | 4 | 641 (222) | 33.9 (12.3 to 65.2) | 99.4 (95.6 to 99.9) | 86.9 (23.6 to 99.0) | 93.1 (90.7 to 96.3) |

Table 5. Xpert Ultra summary sensitivity and specificity by type of specimen, comorbidity status, and reference standard (Continued)

| | | | | | | | |
|----------------------------------|-----------|---|-----------|---------------------|----------------------|---------------------|---------------------|
| Severe malnutrition | MRS | 7 | 1123 (66) | 63.8 (41.0 to 81.7) | 97.6 (94.1 to 99.0) | 74.6 (43.7 to 90.4) | 96.0 (93.5 to 98.0) |
| Severe malnutrition | Composite | 3 | 245 (71) | 39.8 (19.4 to 64.6) | 99.7 (77.4 to 100.0) | 93.1 (08.7 to 99.9) | 93.7 (89.6 to 96.2) |
| Nasopharyngeal aspirate specimen | | | | | | | |
| HIV negative | Culture | 4 | 697 (115) | 64.2 (24.1 to 91.0) | 76.9 (32.6 to 95.8) | 23.6 (03.8 to 70.8) | 95.1 (79.4 to 99.0) |
| HIV negative | Composite | 4 | 476 (306) | 20.4 (09.0 to 40.0) | 99.5 (62.8 to 100.0) | 81.1 (02.6 to 99.9) | 91.8 (86.1 to 93.8) |
| Severe malnutrition | Culture | 7 | 1123 (66) | 63.8 (41.0 to 81.7) | 97.6 (94.1 to 99.0) | 74.6 (43.7 to 90.4) | 96.0 (93.5 to 98.0) |
| Severe malnutrition | Composite | 3 | 245 (71) | 39.8 (19.4 to 64.6) | 99.7 (77.4 to 100.0) | 93.1 (08.7 to 99.9) | 93.7 (89.6 to 96.2) |

^a Predictive values were determined at a pretest probability of 10%.

^b Meta-analysis using univariate fixed-effect or random-effects logistic regression models is not possible when all studies in a meta-analysis report 100% specificity. Therefore, the summary specificity was calculated by dividing the total number of non-cases by the total number of true negatives.

CI: confidence interval; **CLHIV:** children living with HIV; **TB:** tuberculosis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotics, Antitubercular [therapeutic use]; Cross-Sectional Studies; *HIV Infections [drug therapy]; Microbial Sensitivity Tests; *Mycobacterium tuberculosis [genetics]; Rifampin [pharmacology]; Sensitivity and Specificity; Sputum [microbiology]; *Tuberculosis, Lymph Node [diagnosis] [drug therapy]; *Tuberculosis, Meningeal [cerebrospinal fluid] [diagnosis] [drug therapy]; *Tuberculosis, Pulmonary [diagnosis] [drug therapy] [microbiology]

MeSH check words

Adolescent; Child; Humans