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[Diagnostic Test Accuracy Review]

Low-complexity manual nucleic acid amplification tests for pulmonary tuberculosis in children

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ABSTRACT

Background

Accurate and prompt diagnosis of tuberculosis in children is challenging due to non-specific clinical presentation and the low bacillary load of samples. Low-complexity manual nucleic acid amplification tests (LC-mNAATs) such as loop-mediated isothermal amplification (TB-LAMP) are World Health Organization (WHO)-recommended rapid molecular diagnostic tests. Even in resource-limited settings, they have good diagnostic accuracy in adults.

Objectives

To determine the diagnostic accuracy of LC-mNAATs for the detection of pulmonary tuberculosis in children (< 10 years) with presumptive pulmonary tuberculosis.

Secondary objectives

1. To compare the diagnostic accuracy of LC-mNAATs and Xpert MTB/RIF Ultra for the detection of pulmonary tuberculosis in children with presumptive pulmonary tuberculosis.

2. To compare the diagnostic accuracy of LC-mNAATs and smear microscopy for detecting pulmonary tuberculosis in children when TB-LAMP is considered as a replacement test for smear microscopy.

3. To determine the diagnostic accuracy of LC-mNAATs for the detection of pulmonary tuberculosis if used as an add-on test amongst sputum smear-negative children.

4. To investigate potential sources of heterogeneity in the diagnostic accuracy of LC-mNAATs due to factors such as smear status, age, HIV status, setting, and tuberculosis burden.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index, Biosis Previews, Global Index Medicus, SCOPUS, WHO ICTRP, and ClinicalTrials.gov on 2 October 2023 for published articles and trials in progress without language or time limits. We screened the reference lists of included articles, conference abstracts, tuberculosis reviews, and guidelines. We searched ProQuest Dissertations & Theses A&I for dissertations. We approached the Stop TB Partnership, FIND, and other experts on tuberculosis for ongoing and unpublished studies. A WHO public call was made between 30 November 2023 and 15 February 2024 for ongoing and unpublished studies from manufacturers and researchers.

Selection criteria

We included cross-sectional and cohort studies that evaluated LC-mNAATs in children (< 10 years) against microbiological or composite reference standards. Our index test was TB-LAMP, and comparator index tests were Xpert MTB/RIF Ultra and smear microscopy. The microbiological reference standard included automated liquid culture, solid culture, or a combination of both methods. We considered only design-locked, marketed technologies.

Data collection and analysis

Four review authors, in pairs, independently screened titles and abstracts and assessed the full texts of potentially eligible articles. A fifth review author resolved any disagreements. We tailored and applied the QUADAS-2 and QUADAS-C tools to assess the risk of bias and applicability. Six review authors, in three pairs, extracted data and performed methodological quality assessment. A seventh review author resolved any disagreements. We contacted the primary study authors for missing data. We assessed the certainty of evidence using the GRADEpro GDT online tool.

Main results

We included four eligible studies (303 participants). Three studies took place in low- and middle-income countries, with two studies from countries with a high tuberculosis burden. All four studies assessed different respiratory and non-respiratory specimen types and evaluated TB-LAMP against the microbiological reference standard.

We judged one study to have an unclear risk of bias in two domains of QUADAS-2. The risk of bias was low for most of the studies. One study recruited inpatients from tertiary hospitals, causing high applicability concerns.

Three studies (67 children, including eight with pulmonary tuberculosis) evaluated respiratory samples (sputum, broncho-alveolar lavage, and tracheal aspirate). The sensitivities were between 60% and 100%, and the specificities were between 95% and 100% (very low-certainty (sensitivity) and low-certainty (specificity) evidence). Three studies (176 participants, including 14 children with pulmonary tuberculosis) used gastric aspirate; the sensitivity was not estimable in two studies, and was 64% in the third study. The specificities were between 93% and 100%. The sensitivity was 100% (95% confidence interval (CI) 29 to 100), and the specificity was 96% (95% CI 88 to 100) in gastric lavage from one study. One study (144 participants, 12 children with pulmonary tuberculosis) assessed diagnostic accuracy using nasopharyngeal aspirate. The sensitivity was 58% (95% CI 28 to 85), and the specificity was 94% (95% CI 88 to 97). The same study (seven children with pulmonary tuberculosis) also evaluated stool specimens, and the sensitivity and specificity were 100% (95% CI 59 to 100) and 92% (95% CI 86 to 96), respectively. We did not perform a meta-analysis due to limited data.

Interpretation of the results

Respiratory samples

For every 1000 children tested, if 100 had tuberculosis according to culture, 60 to 100 with tuberculosis would be identified as positive by the TB-LAMP. Of the 900 children without tuberculosis, 855 to 900 would be identified as negative by the test.

Gastric aspirate

For every 1000 children tested, if 100 had tuberculosis according to culture, 64 with tuberculosis would be identified as positive by the TB-LAMP. Of the 900 children without tuberculosis, 837 to 900 would be identified as negative by the test.

Gastric lavage

For every 1000 children tested, if 100 had tuberculosis according to culture, 135 would be TB-LAMP positive, of which 100 would have tuberculosis (true positives), and 35 would not have tuberculosis (false positives); 865 would be TB-LAMP negative, of which 864 would not have tuberculosis (true negatives), and one would have tuberculosis (false negatives).

Nasopharyngeal aspirate

For every 1000 children tested, if 100 had tuberculosis according to culture, 112 would be TB-LAMP positives, of which 58 would have tuberculosis (true positives), and 54 would not have tuberculosis (false positives); 888 would test negative, of which 846 would not have tuberculosis (true negatives), and 42 would have tuberculosis (false negatives).

Stool

For every 1000 children tested, if 100 had tuberculosis according to culture, 171 would be TB-LAMP positive, of which 99 would have tuberculosis (true positives), and 72 would not have tuberculosis (false positives); 829 would test negative, of which 828 would not have tuberculosis (true negatives) and one child would have tuberculosis (false negative).

Authors' conclusions

Evidence on the diagnostic accuracy of LC-mNAATs for the detection of pulmonary tuberculosis in children is limited due to few and small studies. Adequately powered studies evaluating LC-mNAATs in children are needed.

PLAIN LANGUAGE SUMMARY

How accurate are low-complexity manual nucleic acid amplification tests for detecting pulmonary tuberculosis in children?

Key messages

- There is limited evidence that LC-mNAATs can correctly identify pulmonary tuberculosis in children.

- Further studies are needed to assess the accuracy of LC-mNAATs among children.

Why is improving the diagnosis of pulmonary tuberculosis among children important?

Tuberculosis in children is frequently under-reported due to the difficulties associated with diagnosing the disease. Early detection and treatment of tuberculosis in children is vital for a timely and effective cure. However, recognising tuberculosis early is difficult due to its varied forms and symptoms, and challenges with producing phlegm (mucus coughed up from the lungs). In addition, bacterial levels in samples are lower than in adults. False-positive results can cause unnecessary anxiety, and children will be followed up, requiring time and resources. These children may also start tuberculosis treatment with severe side effects. False-negative results may result in missed cases, leading to the spread of the disease. Children with false-negative results may also develop severe forms of tuberculosis, leading to death due to delayed diagnosis.

What are low-complexity manual nucleic acid amplification tests for detecting tuberculosis?

One of the tests used for detecting tuberculosis is TB-LAMP (loop-mediated isothermal amplification), which belongs to a category known as low-complexity manual nucleic acid amplification tests (LC-mNAATs). These tests can be used in places with relatively simple infrastructure, similar to what is needed for sputum microscopy (microscope examination of mucus coughed up from the lungs). They are more accurate than tests with sputum or other respiratory samples, even when the bacterial count is low, and give results in a few hours. At present, there is a lack of evidence on the accuracy of the TB-LAMP test in detecting tuberculosis in children.

What did we want to find?

We wanted to find out how accurate LC-mNAATs are for detecting pulmonary tuberculosis in children presumed to have pulmonary tuberculosis and compare the accuracy with Xpert MTB/RIF Ultra and smear microscopy.

What did we do?

We searched for studies that investigated the accuracy of LC-mNAATs in detecting pulmonary tuberculosis in children and examined the results of relevant studies.

What did we find?

We included four studies (303 participants, 25 children with tuberculosis) that evaluated TB-LAMP. One study compared the accuracy of TB-LAMP and Xpert MTB/RIF Ultra, and three studies also used smear microscopy. These studies used multiple respiratory and non-respiratory specimens to detect tuberculosis. All studies used culture as the reference standard, the best available way of identifying the presence of tuberculosis.

Respiratory samples

Three studies (67 children, eight positive for tuberculosis) used respiratory samples (sputum (phlegm), bronchoalveolar lavage (fluid obtained after washing the airway and lungs), and tracheal aspirate (fluid obtained from the windpipe)). The results indicate that 60% to 100% of children with tuberculosis will be identified as positive by the TB-LAMP test, and 95% to 100% of children without tuberculosis will be identified as negative by the test.

Gastric aspirate (fluid obtained from the stomach using a tube)

Three studies used gastric aspirate samples (176 children, 14 positive for pulmonary tuberculosis). The results indicate that 64% of children with tuberculosis will be identified as positive by the TB-LAMP test, and 35% to 87% of children without tuberculosis will be identified as negative by the test.

Gastric lavage (fluid obtained from the stomach using a tube after a wash)

One study with 60 children (three positive for tuberculosis) evaluated gastric lavage. For every 1000 children tested, if 100 had tuberculosis according to culture, 135 would be TB-LAMP positive, of which 99 would have tuberculosis, and 36 would not have tuberculosis; 865 would be TB-LAMP negative, of which 864 would not have tuberculosis, and one would have tuberculosis.

Nasopharyngeal aspirate (fluid obtained from the back of the nose and throat)

One study (144 children, 12 positive for tuberculosis) evaluated nasopharyngeal aspirate. For every 1000 children tested, if 100 had tuberculosis according to culture, 71 would be TB-LAMP positive, of which 12 would have tuberculosis, and 59 would not have tuberculosis; 929 would test negative, of which 921 would not have tuberculosis, and eight would have tuberculosis.

Stool

One study evaluated stool specimens (144 children, seven positive for pulmonary tuberculosis). For every 1000 children tested, if 100 had tuberculosis according to culture, 171 would be TB-LAMP positive, of which 99 would have tuberculosis, and 72 would not have tuberculosis; 829 would test negative, of which 828 would not have tuberculosis, and one child would have tuberculosis.

What are the limitations of the evidence?

We did not find any study that used a composite reference standard (the results of different tests are combined and considered as a confirmatory test). Since culture is not the best way to determine the disease in children, our evidence is limited. The results come from four studies with a small number of children, and the findings are likely to change as more studies become available.

How up-to-date is this evidence?

The evidence is up-to-date to October 2023.

SUMMARY OF FINDINGS

Summary of findings 1. LC-mNAAT in respiratory samples for the detection of pulmonary tuberculosis in children (0 to 9 years)

Review question: Should LC-mNAAT on respiratory samples be used to diagnose pulmonary tuberculosis in children with signs and symptoms of pulmonary tuberculosis using a microbiological reference standard?

Population: children (< 10 years) with signs and symptoms of pulmonary tuberculosis

Role: as an initial diagnostic test

Index test: LC-mNAAT (TB-LAMP)

Threshold for index test: a preset threshold is incorporated in the kit based on the quantity of the amplified DNA both for the visual detection method and for quantitative estimation using turbidimetry

Reference standard: solid or liquid culture

Study design: cross-sectional

Setting: primary care facilities and peripheral labs

Limitations: a summary estimate could not be provided owing to insufficient data

Range of sensitivities: 0.60 to 1.00

Range of specificities: 0.95 to 1.00

Test results	Number of results per 1000 participants tested (ranges)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 1%	Prevalence 5%	Prevalence 10%		
True positives	6 to 10	30 to 50	60 to 99	8 (3)	⊕◯◯◯ **Very low**[a,b,c]
False negatives	0 to 4	0 to 20	1 to 40		
True negatives	941 to 980	903 to 941	855 to 891	59 (3)	⊕⊕◯◯ **Low**[a,d]
False positives	10 to 49	9 to 47	9 to 45		

Footnotes
Meta-analysis was not performed. Intervals displayed are ranges derived from the minimum and maximum reported sensitivity and specificity.
CI: confidence interval
Explanations
Prevalence levels of pulmonary tuberculosis in the table were suggested by the WHO Global Tuberculosis Programme.

[a]Median prevalence (11%; range 6% to 33%) in the included studies was above the range of the three prevalence values provided in the GRADE tables. Of the three studies, one study recruited participants from the inpatient setting of a tertiary care hospital. We downgraded by one level for indirectness.
[b]The point estimates for sensitivity were 60%, 100%, 100%; although the 95% CIs overlapped, they were very wide. We downgraded by one level for inconsistency and one level for imprecision.
[c]A very small number of children with pulmonary tuberculosis contributed to the analysis of the observed sensitivities and the 95% CI for each study was very wide. We downgraded by one level for imprecision.
[d]A small number of children contributed to this analysis for the observed specificities. Of the three studies, one study had a wide 95% CI (40% to 100%) for specificity estimation. We downgraded by one level for imprecision.
GRADE certainty of the evidence
High: We are very confident that the true effect is close to the estimate of the effect.
Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: Our confidence in the effect estimate is limited; the true effect may differ substantially from the estimate.
Very low: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

Summary of findings 2. LC-mNAAT in stool samples for the detection of pulmonary tuberculosis in children (0 to 9 years)

Review question: Should LC-mNAAT on stool be used to diagnose pulmonary tuberculosis in children with signs and symptoms of pulmonary tuberculosis using a microbiological reference standard?

Population: children (< 10 years) with signs and symptoms of pulmonary tuberculosis

Role: as an initial diagnostic test

Index test: LC-mNAAT (TB- LAMP)

Threshold for index test: a preset threshold is incorporated in the kit based on the quantity of the amplified DNA both for the visual detection method and for quantitative estimation using turbidimetry

Reference standard: solid or liquid culture

Study design: cross-sectional

Setting: primary care facilities and peripheral labs

Limitations: a summary estimate could not be provided owing to insufficient data

Single study sensitivity: 1.00 (95% CI 0.59 to 1.00)

Single study specificity: 0.92 (95% CI 0.86 to 0.96)

Test result	Number of results per 1000 participants tested (95% CI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 1%	Prevalence 5%	Prevalence 10%		
True positives	**10** (6 to 10)	**50** (30 to 50)	**99** (59 to 99)	7 (1)	⨁◯◯◯ **Very low**[a,b]

False negatives	**0** (0 to 4)	**0** (0 to 20)	**1** (1 to 41)		
True negatives	**911** (851 to 950)	**874** (817 to 912)	**828** (774 to 864)	137 (1)	⊕⊕◯◯ **Low**[a]
False positives	**79** (40 to 139)	**76** (38 to 133)	**72** (36 to 126)		

Footnotes

CI: confidence interval

Explanations

Prevalence levels of pulmonary tuberculosis in the table were suggested by the WHO Global Tuberculosis Programme.

[a]One study contributed data for this analysis. The study was done in Cameroon, which does not have a high tuberculosis burden, with 30% of participants being children with HIV. We downgraded by two levels for indirectness due to applicability concerns in other settings.

[b]A very small number of children with pulmonary tuberculosis contributed to the observed sensitivity, and the 95% CI (59% to 100%) was very wide. We downgraded by two levels for imprecision.

GRADE certainty of the evidence

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

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

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

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

BACKGROUND

Tuberculosis, one of the deadliest diseases, was the second leading cause of death after COVID-19 in 2022. Globally, the number of people newly diagnosed with tuberculosis was 8.2 million in 2023, up from 7.5 million in 2022. In 2023, the highest number of tuberculosis cases was recorded since the World Health Organization (WHO) commenced global monitoring of the disease in 1995 (WHO Global TB report 2024). The highest burden was among adult men, with an estimated 6 million cases. However, 12% of the total cases were contributed by children and young adolescents (0 to 14 years), amounting to approximately 1.3 million cases in 2023 (WHO Global TB report 2024). The apparent fall in the number of tuberculosis cases in 2020 and 2021 was primarily due to the COVID-19 pandemic disrupting essential tuberculosis services. The decline in the number of tuberculosis cases likely reflects the growing number of people who were undiagnosed and untreated. Underdiagnosis may result in death and increased transmission of tuberculosis in the community (WHO Global TB report 2022). Overall, tuberculosis caused 1.25 million deaths in 2023, of which 166,000 were among children (WHO Global TB report 2024).

Multiple factors contribute to diagnostic delays and the consequent rise in incidence and mortality among children. The unique pathophysiology and clinical manifestations of tuberculosis in children make diagnosis particularly difficult. First, tuberculosis in children may resemble several common childhood illnesses, such as pneumonia, bacterial and viral infections, malnutrition, and HIV. Second, the disease is caused by a small number of bacteria (paucibacillary), which reduces diagnostic yield in various biological specimens. Third, younger children produce a smaller amount of sputum than adults, which is generally swallowed rather than expectorated. Children may require hospital admission with overnight fasting for gastric washings and may require repeat sampling, which is considered an unpleasant procedure and challenging to perform in limited resource settings. Finally, of the children with presumptive tuberculosis, only about 6.8% (95% confidence interval (CI) 2.2% to 12%) are positive on acid-fast bacilli (AFB) smear, with children under five years having an even lower rate of 0.5% (95% CI 0% to 1.9%) and 30% to 40% are culture-positive (Kunkel 2016). Treating physicians often rely on clinical judgement, using signs and symptoms, contact history, chest x-ray, and tuberculin skin testing to diagnose tuberculosis in children (Nicol 2011; Swaminathan 2010). The clinical criteria still have a risk of missing a sizeable number of tuberculosis cases in children. Timely diagnosis of tuberculosis in children is crucial, not only to prevent complications and mortality, but also to measure the ongoing transmission of *Mycobacterium tuberculosis,* as childhood tuberculosis is a good indicator of recent and ongoing transmission in the community (Schepisi 2019; Silva 2021). Therefore, the newer rapid molecular-based diagnostic methods could improve tuberculosis detection and reduce diagnostic delays.

The newer, more rapid, and more sensitive molecular tests recommended by the WHO for the initial detection of *Mycobacterium tuberculosis* complex and drug resistance are mWRDs (molecular WHO-recommended rapid diagnostic tests). The mWRDs include "Xpert MTB/RIF Ultra and Xpert MTB/RIF (Cepheid, Sunnyvale, United States of America [USA]), Truenat MTB Plus and MTB-RIF Dx tests (Molbio Diagnostics, Goa, India), and loop-mediated isothermal amplification (TB-LAMP; Eiken Chemical, Tokyo, Japan)" (WHO 2024). The WHO has recommended replacing smear microscopy with mWRD wherever possible (WHO 2016b). The WHO groups individual tests with similar characteristics and performance into a class. The classes are defined by the "type of technology (e.g., automated or reverse hybridization nucleic acid amplification tests [NAATs]), the complexity of the test for implementation (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, detection of resistance to first-line or second-line drugs)" (WHO 2024). Currently, low-complexity automated nucleic acid amplification tests (LC-aNAATs), such as Xpert assays, are most preferred given their sensitivity and specificity, rapid turnaround time, and ability to detect rifampicin resistance simultaneously. However, the use of LC-aNAATs is challenging in resource-limited settings owing to the high cost of the equipment, cartridges, or chips and the requirement for laboratory infrastructure. These challenges could be mitigated by low-complexity manual nucleic acid amplification tests (LC-mNAATs), such as tuberculosis loop-mediated isothermal amplification (TB-LAMP).

TB-LAMP can serve as an alternative to smear microscopy in resource-limited settings due to its similar biosafety requirements and infrastructure needs. It features a quick turnaround time, resistance to sample matrix inhibitors, high product yield, and low cost. This diagnostic tool may be a more efficient option than microscopy for detecting tuberculosis in children in low- and middle-income countries. TB-LAMP was reported to have higher sensitivity and lower specificity than smear microscopy amongst children, where induced sputum, gastric aspirate, or bronchoalveolar lavage fluid (BALF) was used for the diagnosis of tuberculosis (Fan 2022). Similarly, various studies of adults with tuberculosis have demonstrated TB-LAMP to have higher sensitivity and specificity than smear microscopy (Joon 2017).

Pulmonary tuberculosis

Tuberculosis is a disease caused by the infection of *Mycobacterium tuberculosis,* which affects all ages. It primarily affects the respiratory system, causing the pulmonary form of the disease (pulmonary tuberculosis). The bacteria also affect other organ systems and cause extrapulmonary tuberculosis. Individuals can harbour the infection in their body without any symptoms, which, when diagnosed, is identified as latent tuberculosis infection (LTBI), while individuals exhibiting symptoms are diagnosed as having active tuberculosis disease.

Children and adolescents are at a higher risk of progression to the disease following infection with *M tuberculosis*, with increased susceptibility amongst the under-five age group. Ninety per cent of tuberculosis disease among children is estimated to occur within one year of infection (Marais 2014). Factors such as age, maturity of the immune system, host genetic factors, and comorbidities such as HIV and nutritional status play a role in various presentations, from containing the infection to manifesting as a disseminated disease in children (Franco 2024; Moore 2024). The most common risk factor in high-burden countries for tuberculosis is having household contact with bacteriologically confirmed tuberculosis. Studies have documented that more than 20% of children with tuberculosis had a history of contact with tuberculosis cases at home in high-burden settings (Martinez 2020; Pasqualini 2023).

The clinical spectrum of tuberculosis in children may range from asymptomatic primary infection, symptomatic tuberculosis disease, and extrapulmonary manifestations to disseminated tuberculosis or adult-type disease (Marais 2011). It takes approximately one to three months to develop adaptive immune responses for the detection of infection after exposure to a potential source of infection. During this period of development of the primary lesion (termed Ghon's focus) in the lung parenchyma and spread to hilar and mediastinal nodes (Ghon's complex), the symptoms are primarily non-respiratory, mild, and self-limiting. Further to the failure of containment of infection in these areas, children may develop the disease in the intrathoracic lymph nodes or lung parenchyma and present with systemic and respiratory symptoms (Thomas 2017). Adult cavitary-type diseases (abnormal hollow spaces within the pulmonary parenchyma) are more likely to present in older children. The symptoms include a low-grade fever, non-productive cough, loss of weight, and non-specific symptoms such as wheezing due to compression of the bronchi by lymph nodes or reduced size of the bronchial lumen by granulomas and croup in the case of laryngeal involvement (Piccini 2014).

Along with laboratory investigations, chest imaging (chest X-ray, computerised tomography) plays a significant role in the diagnosis of pulmonary tuberculosis. The abnormalities observed in imaging are often broad and non-specific; however, the presence of specific patterns (Ghon's focus, hilar adenopathy, miliary pattern, cavities, etc.), in addition to clinical features, is often suggestive of tuberculosis disease (Roya-Pabon 2016). Given the varied presentations of pulmonary tuberculosis in children across different age groups and non-specific observations in imaging, children are often misdiagnosed, leading to delays in diagnosis and mismanagement.

The WHO recommends a four-month treatment plan that includes isoniazid (H), rifampicin (R), and pyrazinamide (Z) in the first two months (2HRZ(E)/2HR) for children and adolescents with non-severe tuberculosis who are three months to 16 years old (without suspicion or evidence of drug-resistant tuberculosis). Ethambutol (E) should only be used in places where there is a high burden of HIV or isoniazid resistance. Tuberculosis in peripheral lymph nodes, intrathoracic lymph node tuberculosis without airway obstruction, uncomplicated pleural effusion, non-cavitary disease confined to a single lung lobe, and non-miliary patterns are regarded as non-severe tuberculosis. Children and adolescents who do not meet the criteria for non-severe tuberculosis or who have severe tuberculosis, as well as infants aged zero to three months, are recommended to be treated with standard six-month treatment (2HRZE/4HR). Children over the age of 12 years with drug-susceptible pulmonary tuberculosis may be administered a regimen with H, rifapentine (P), moxifloxacin (M), and Z (2HPMZ/2HPM) for four months (WHO 2022a).

Index test(s)

The index test is a low-complexity manual nucleic acid amplification test (LC-mNAAT), and the most common LC-mNAAT is TB-LAMP. TB-LAMP was developed and marketed by Eiken Chemicals (Tokyo, Japan) (Eiken 2019). Other TB-LAMP kits that are commercially available are the Nu-LAMP TB kit of RAS Lifescience Private Limited, India and RealAmp, developed by DEAOU Biotech Company Limited, Guangzhou, China. The comparator index tests are Xpert MTB/RIF Ultra assay and smear microscopy. Cepheid (Cepheid Inc, a subsidiary of Danaher Corp, Sunnyvale, USA) developed the Xpert MTB/RIF Ultra assay (Cepheid 2022a). Smear microscopy includes the Ziehl-Neelsen stained smears examined under a light microscope and auramine-phenol-stained smears performed under fluorescence microscopy.

TB-LAMP is based on an amplification process that uses four primers matching the target gene's six locations and a strand displacement reaction at 65 °C for 15 to 60 minutes. An improved amplification process of 10^9 to 10^{10} times can be achieved by using loop primers in the TB-LAMP assay (WHO 2016b). Since this assay is insensitive to the build up of DNA and pyrophosphate salt by-products, it can continue until a substantial amount of amplicons has been produced. This also makes the amplification process visible to the naked eye using double-stranded DNA dyes, such as SYBR Green. The assay can be completed within one hour and consists of three steps: sample preparation (10 to 20 minutes), amplification (40 minutes), and visual detection of fluorescence using ultraviolet light (0.5 to 1 minute). Evaluation of the TB-LAMP assay's operational feasibility was carried out in various peripheral settings, and it was shown that technicians without molecular training could conduct the tests with high reproducibility in a basic laboratory environment without specialised equipment (Boehme 2007; Gray 2016). The summary sensitivity of this test from 13 diagnostic accuracy studies among adult participants conducted in high- and low-burden settings was 80.3% (95% CI 70 to 88), and the summary specificity was 97.7% (95% CI 96 to 99) (WHO 2016b). However, no systematic review or evidence is available on the diagnostic accuracy of TB-LAMP among children. It is also important to note that one of the significant disadvantages of TB-LAMP is its inability to detect rifampicin resistance.

Comparator index tests

Xpert assays detect the presence of both *M tuberculosis* and rifampicin resistance in a single step, combining the sample processing and the amplification process in a closed Xpert system. The Xpert MTB/RIF Ultra assay was designed to detect *M tuberculosis* complex with greater sensitivity than the Xpert MTB/RIF assay. Xpert/RIF Ultra has superseded Xpert MTB/RIF due to its better sensitivity. Xpert MTB/RIF Ultra has two distinct multicopy amplification targets (*IS6110* and *IS1081*) and improvements in cartridge design and assay chemistry. These changes reduced the lower detection limit by 10-fold compared to the threshold level of Xpert MTB/RIF (Chakravorty 2017). Analytical data from the laboratory also indicated enhanced discrimination of silent mutations and identification of rifampicin resistance in cases of mixed infection. The test procedure can be completed in 1 to 1.5 hours. The sample processing involves mixing the reagent with the sputum sample in a ratio of 2:1 for a direct specimen and 3:1 for processed pellets (Chakravorty 2017). After an incubation period of 15 minutes, the processed mixture is loaded into the cartridge and placed in the machine.

The summary sensitivity of Xpert MTB/RIF Ultra (90.9%, 95% credible interval (CrI) 86.2 to 94.7) was higher than that of Xpert MTB/RIF (84.7%, 95% CrI 78.6 to 89.9). Conversely, the summary specificity of Xpert MTB/RIF Ultra was lower (95.6%, 95% CrI 93.0 to 97.4) compared to that of Xpert MTB/RIF Ultra (98.4%, 95% CrI 97.0 to 99.3) in adults (Zifodya 2021). In children, the summary sensitivity of Xpert MTB/RIF Ultra was 75.3% (95% CI 64.3 to 83), and summary specificity was 97.1% (95% CI 94.7 to 98.5) against culture in sputum specimens. In gastric aspirate, the summary sensitivity

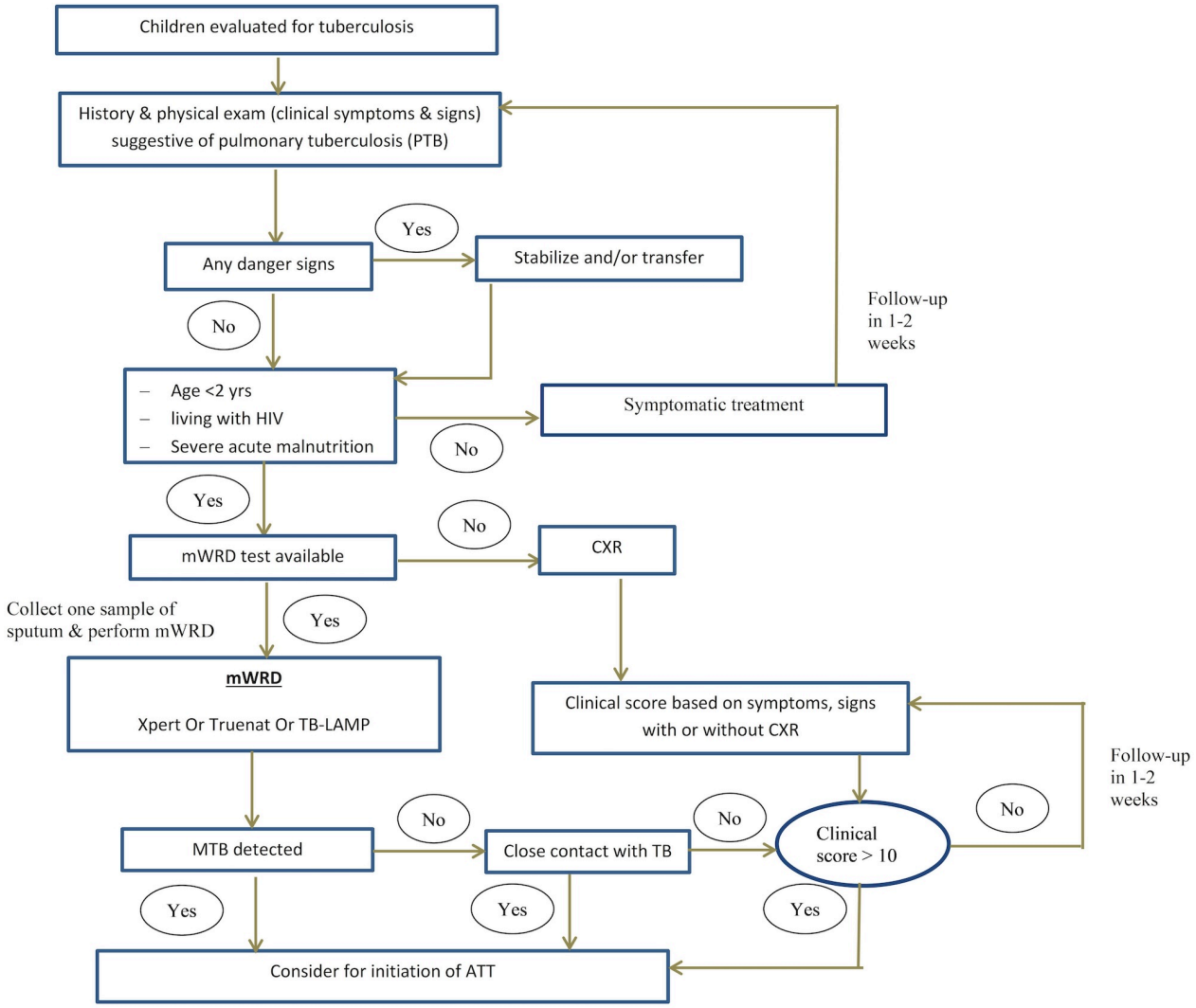
and specificity was 70.4% (95% CI 53.9 to 82.9) and 94.1% (95% CI 84.8 to 97.8), respectively, against culture (Kay 2022).

Despite the WHO recommendations against the use of smear microscopy for AFB in sputum, in many countries it is still used as one of the initial diagnostic tools for detecting *M tuberculosis* in children (WHO 2023). Even though smear microscopy has advantages such as lower turnaround time, easy use in low-resource settings, and cost-effectiveness, its lower sensitivity (50% to 60%) is a significant limitation for using it as a diagnostic test. Further, poor performance is documented in children, especially those under five years of age, with sensitivity ranging from 7% to 40% (Cuevas 2012). A systematic review on smear positivity documented that the summary percentage of smear positivity amongst children was 6.8% (95% confidence interval (CI) 2.2 to 12.2) compared to 52% (95% CI 40 to 64) in adults. Moreover, the percentage of smear positivity further reduced to 0.5% under the age of four years (Kunkel 2016). These findings clearly indicate the risk of missing the diagnosis of tuberculosis in children while using smear microscopy in tuberculosis programmes. With this limitation of reduced sensitivity, the WHO has recommended replacing smear microscopy with either Xpert MTB/RIF or Xpert MTB/RIF Ultra in children with symptoms of pulmonary tuberculosis in its recent guidelines (WHO 2024).

Clinical pathway

The clinical pathway and the context in which the index test and comparator index tests may be used are described in Figure 1. Children and adolescents are at higher risk of contracting tuberculosis if their household contacts have bacteriologically confirmed tuberculosis. Other risk factors are HIV and severe acute malnutrition. Symptoms such as unremitting cough, prolonged fever, anorexia, failure to thrive or weight loss, tiredness, decreased activity, and reduced playfulness or alertness are typical of pulmonary tuberculosis in children (WHO 2014). If these symptoms persist for more than two weeks, they are considered to be presumptive tuberculosis (WHO 2022a). Examples of unusual presentations of tuberculosis in children include acute severe pneumonia in those under two years of age. Children living with HIV or those exhibiting a fixed airway wheeze that does not respond to bronchodilator therapy, particularly those under five years of age, may also present with unusual symptoms (Graham 2016; WHO 2022a).

Figure 1. Clinical pathway for diagnosis of paediatric pulmonary tuberculosis (WHO 2022b) Abbreviations: CXR: chest x-ray; LTBI: latent tuberculosis infection; MTB: *Mycobacterium tuberculosis*; mWRD: molecular WHO-recommended rapid diagnostic test; PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TPT: tuberculosis preventive treatment; Truenat: means Truenat MTB or Truenat MTB Plus assays; TST: tuberculin skin test; Xpert: refers to Xpert MTB/RIF or Xpert Ultra assays.



The WHO has recommended integrated algorithms for making treatment decisions in children with presumptive pulmonary tuberculosis. The first step is determining if the child has any symptoms or signs indicating a medical urgency. Children with danger signs should be referred to a higher level of care. After stabilising, the child should be evaluated for tuberculosis (WHO 2016a; WHO 2022b). While it is crucial to attempt microbiological confirmation, young children cannot expectorate adequate sputum samples, and their sputum is usually paucibacillary, leading to reduced sensitivity of the diagnostic tests. Older children (aged five to nine years) and adolescents (aged 10 to 18 years) are more likely to have an adult-type disease that is positive on bacteriological testing (WHO 2014). Despite these challenges, bacteriological confirmation must be sought using mWRDs such as Xpert MTB/RIF Ultra, Truenat, or TB-LAMP. Alternative types of samples obtained using non-invasive methods are vital in diagnosing tuberculosis in children. The WHO recommends the use of sputum, gastric aspirates, nasopharyngeal aspirates, or stool samples for Xpert assays (WHO 2024). However, only sputum samples have been recommended for other mWRDs, such as TB-LAMP. The specimen type chosen is determined by the acceptability and feasibility of collecting the specimens, as well as the availability of the test (WHO 2024).

When bacteriological tests are negative, a chest X-ray can support the clinical diagnosis of pulmonary tuberculosis. Most children with pulmonary tuberculosis have characteristic radiographic changes (WHO 2022a). Young children should have chest X-rays with an anteroposterior view, while older children and adolescents should have chest X-rays with a posteroanterior view. Quality images, including a lateral view and accurate interpretation by a trained healthcare worker in chest X-ray reading, are essential for correct diagnosis (Graham 2016; WHO 2014).

Considering the challenges in microbiological confirmation of tuberculosis in children, the WHO has recommended clinical scoring based on clinical and radiological features (Table 1). Children with clinical scores of 10 or greater should be started on tuberculosis treatment with a regimen recommended by the WHO. Children with scores lower than 10 should be treated symptomatically and followed up one to two weeks later for a repeat clinical assessment. Isoniazid resistance, in addition to rifampicin resistance, is termed multidrug-resistant tuberculosis. If mWRD detects rifampicin resistance, the child is considered to have drug-resistant tuberculosis and is started on treatment for drug-resistant tuberculosis. However, if rifampicin resistance is not detected, the child is treated with the regimen for drug-sensitive tuberculosis (WHO 2022c).

Setting of interest

We were interested in evaluating the performance of the index test, regardless of whether it was conducted in peripheral or central area laboratories. We expected that the laboratory setting would not affect the performance of LC-mNAATs. However, we were particularly interested in the performance of LC-mNAATs in peripheral-level laboratories, which were likely to be associated with primary healthcare facilities. The WHO has set a benchmark in its latest document that all primary healthcare facilities should have access to mWRDs to enable early diagnosis instead of referral to higher facilities because almost 80% of the population seek health care at primary care facilities (WHO 2023). The WHO recommends using the TB-LAMP test to replace or follow smear microscopy in adults with presumptive tuberculosis (WHO 2016b). Therefore, we were interested in determining whether LC-mNAATs such as TB-LAMP could replace smear microscopy for the diagnosis of tuberculosis in children as an initial diagnostic test in primary healthcare facilities and in settings where low-complexity automated nucleic acid amplification tests (LC-aNAATs) such as Xpert MTB/RIF Ultra testing would not be feasible.

Alternative test(s)

In addition to the index test and comparator index tests, several diagnostic tests for pulmonary tuberculosis in children are available. These tests include culture techniques and molecular assays such as Truenat, line probe assays, and lipoarabinomannan (LAM) assays.

Mycobacterial culture is the reference standard for tuberculosis diagnosis with a limit of detection (LOD) of 10 colony-forming units (CFU)/mL to 100 CFU/mL in both solid and liquid media. The solid media generally used for *M tuberculosis* detection is Löwenstein Jensen's (LJ) medium, and the liquid media used is a Mycobacterial Growth Indicator Tube (MGIT) with supplements and antibiotics (Thomas 2017). Compared to the expectorated sputum, the isolation rate of *M tuberculosis* by culture is higher in other specimens, such as induced sputum, gastric lavage, bronchoalveolar lavage, and nasopharyngeal aspirates in children (Hatherill 2009; Thomas 2017). One systematic review by Oliwa and colleagues reported *M tuberculosis* as a culture-confirmed pathogen in 7.5% to 12% of children under five years of age from tuberculosis-endemic regions (Chisti 2013; Oliwa 2015). However, culture sensitivity is generally low, ranging from 7% to 40% due to its paucibacillary nature in this population (Nicol 2011; Thomas 2014). Hence, the WHO recommends the use of molecular tests such as Xpert assays rather than conventional bacteriological methods such as smear and culture for *M tuberculosis* diagnosis in children (WHO 2024).

Truenat assays are one of the rapid molecular tests developed by Molbio Diagnostics in Bangalore, India. Truenat assays include Truenat MTB, Truenat MTB Plus, and Truenat MTB-RIF Dx. The Truenat and Xpert assays can both detect dead and live bacilli in the test sample. Truenat MTB targets the ribonucleoside-diphosphate reductase B single-copy gene (*nrdB*), and Truenat MTB Plus uses multiple targets, *nrdZ and* IS*6110*, to identify *M tuberculosis* complex. Truenat assays were reported to have 73% sensitivity (95% CI 67 to 78) for Truenat MTB and 80% sensitivity (95% CI 75 to 84) for Truenat MTB Plus. Specificities were 98% (95% CI 97 to 99) and 96% (95% CI 95 to 97) for Truenat MTB and MTB Plus, respectively (Penn Nicholson 2021). A study conducted in India demonstrated a sensitivity and specificity of 58.7% (95% CI 47 to 70) and 87.5% (95% CI 84 to 90) against MGIT for the detection of pulmonary tuberculosis among individuals under 18 years old (Singh 2023).

The molecular methods used to detect pulmonary tuberculosis in children may also include stool specimens as the source sample rather than the standard respiratory samples (DiNardo 2018). A hemi-nested PCR (polymerase chain reaction) developed in 2010 targeting the *IS6110* region of *M tuberculosis* showed 86% sensitivity and 100% specificity in stool specimens compared with sputum culture (Cordova 2010). A TruTip technology-based real-time PCR targeting the same *IS6110* region had 59% sensitivity in culture-confirmed tuberculosis (Mesman 2019). Apart from Xpert assays, line probe assays (LPA) are also used to detect resistance to rifampicin and isoniazid. They include GenoType MTBDR*plus,* Hain Lifescience, Nehren, Germany, and the NTM +MDRTB Detection Kit, Nipro Corporation Osaka, Japan. The WHO has recommended using LPAs as follow-up diagnostic tests after tuberculosis confirmation (WHO 2024). Only a few studies have documented the performance of LPAs in detecting drug resistance in children with pulmonary tuberculosis (Arora 2017; Cruz 2013; Ebonyi 2020).

The only WHO-recommended biomarker that could be easily detected in urine is the lipoarabinomannan (LAM) antigen found on the surface of the mycobacterial cell wall (Correia-Neves 2019; WHO 2019). In recent years, tests based on this LAM antigen have been developed, such as the Alere Determine TB LAM by Abbott Laboratories and the Fujifilm SILVAMP TB-LAM test (FujiLAM) (Bulterys 2019). Based on one systematic review, the sensitivity of these tests in HIV-negative children with pulmonary tuberculosis aged less than 15 years was 32.33% (95% CI 7.63 to 57.03) for the Determine TB-LAM Ag test and 50.95% (95% CI 27.45 to 74.45) for FujiLAM (Seid 2022).

Rationale

The newer rapid molecular-based diagnostic tests have significantly reduced diagnostic delays and increased tuberculosis detection. LC-mNAATs such as TB-LAMP may be a suitable alternative in settings without the adequate infrastructure needed to run the LC-aNAAT assays such as Xpert and Truenat assays. TB-LAMP amplifies DNA using temperature-independent methods. It is a novel molecular test that is simple to use, easily read, and requires minimal laboratory infrastructure. It has biosafety requirements similar to smear microscopy and hence could be performed at remote health centres (Boehme 2007).

In 2016, the WHO issued TB-LAMP policy guidance based on evidence generated from 13 diagnostic test accuracy studies conducted in 17 countries. This review showed that TB-LAMP had similar sensitivity and specificity compared to Xpert MTB/RIF; however, compared to smear microscopy, TB-LAMP had similar specificity and higher sensitivity (Shete 2019). Based on these findings, the WHO recommended that TB-LAMP could replace smear microscopy to diagnose pulmonary tuberculosis or to follow up on smear-negative tuberculosis (WHO 2016b).

The WHO extrapolated the recommendations for children from those of adults due to inadequate primary studies in children (WHO 2016b). There has been no systematic review of the diagnostic accuracy of TB-LAMP for tuberculosis in children. With the availability of new studies, we synthesised evidence on the diagnostic accuracy of LC-mNAATs in children to inform part of the 2024 update of the WHO policy guideline on rapid NAATs for tuberculosis detection.

OBJECTIVES

To determine the diagnostic accuracy of LC-mNAATs for the detection of pulmonary tuberculosis in children (< 10 years) with presumptive pulmonary tuberculosis.

Secondary objectives

1. To compare the diagnostic accuracy of LC-mNAATs and Xpert MTB/RIF Ultra for the detection of pulmonary tuberculosis in children with presumptive pulmonary tuberculosis.

2. To compare the diagnostic accuracy of LC-mNAATs and smear microscopy for detecting pulmonary tuberculosis in children when TB-LAMP is considered as a replacement test for smear microscopy.

3. To determine the diagnostic accuracy of LC-mNAATs for the detection of pulmonary tuberculosis if used as an add-on test amongst sputum smear-negative children.

4. To investigate potential sources of heterogeneity in the diagnostic accuracy of LC-mNAATs due to factors such as smear status, age, HIV status, setting, and tuberculosis burden.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional and cohort studies of the diagnostic accuracy of TB-LAMP against culture or composite (or both) reference standards. To compare TB-LAMP and Xpert MTB/RIF Ultra, we included comparative diagnostic accuracy studies in which each participant received both tests (paired design). We included studies that performed the tests using different types of specimens, such as sputum, nasopharyngeal aspirate, gastric aspirate, gastric lavage, and stool, for confirmation of diagnosis. We only included studies that reported the number of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) or provided statistics that enabled their derivation. We excluded studies with a multiple-group design because these studies might lead to biased estimates of diagnostic accuracy.

Participants

Age definitions in prior Cochrane reviews classified children as 14 years and younger and adults as 15 years and older. The current review adheres to guidance from the WHO Department of Maternal, Newborn, Child, and Adolescent Health and Ageing and the WHO Global Tuberculosis Programme. The new definition categorises those aged 10 years and under as children, those aged 10 to 19 as adolescents, and individuals aged 20 years and above as adults (WHO 2022a). We included studies that evaluated TB-LAMP for diagnosing pulmonary tuberculosis in children aged between zero and nine years who presented with presumptive tuberculosis. Children with cough, fever, poor appetite or anorexia, weight loss or failure to thrive, fatigue, reduced playfulness, or decreased activity for more than two weeks were presumed to have tuberculosis (WHO 2014). Children with and without chest x-ray abnormalities were included. We included both HIV-negative and HIV-positive children. We included children whose respiratory specimens were collected by various means, such as expectorated or induced sputum and gastric and nasopharyngeal aspirates. Gastric specimens could be obtained by gastric aspiration, lavage, or washing. We included children from inpatient and outpatient settings. We also included stool specimens. We included studies from all levels of healthcare settings and peripheral and intermediate laboratories. We included studies from community and healthcare facilities, irrespective of the burden of tuberculosis in those settings. We placed no restrictions on gender or geographical location. If a study included children and adolescents or adults, and if disaggregated data were not available in the published paper, we contacted the study authors for the data. If the study authors declined, did not respond, or data were not available, we excluded such studies.

Index tests

The index test was TB-LAMP, and the comparator index tests were the Xpert MTB/RIF Ultra assay and smear microscopy. TB-LAMP results are interpreted qualitatively by visual detection (green fluorescence) or quantitatively by turbidity measurement using real-time turbidimetry, as per manufacturer recommendations (Eiken 2019). We included only design-locked, marketed TB-LAMP assays. Xpert MTB/RIF Ultra results are automatically generated, and the user is provided with a printable test result, which is as follows:

1. MTB (*Mycobacterium tuberculosis*) DETECTED; Rif (rifampicin) resistance DETECTED
2. MTB DETECTED; Rif resistance NOT DETECTED
3. MTB DETECTED; Rif resistance INDETERMINATE
4. MTB NOT DETECTED
5. INVALID/ERROR/NO RESULT

Invalid, error, and no result indicate that the presence or absence of *M tuberculosis* could not be determined (Kay 2020). Xpert MTB/RIF Ultra also incorporates a semi-quantitative classification for results: trace, very low, low, moderate, and high. We considered 'trace' as positive for *M tuberculosis* (WHO 2017). One of the secondary objectives was also to compare the diagnostic accuracy of LC-mNAAT and smear microscopy. We considered smear microscopy, either Ziehl-Neelsen microscopy, fluorescence microscopy, or both microscopy methods. Microscopy was graded negative, scanty, 1+, 2+, or 3+ based on standard guidelines (CTD 2016). We considered the result as positive if at least one AFB was identified in any smear.

Target conditions

The target condition was active pulmonary tuberculosis.

Reference standards

1. Culture

We used culture as a reference standard for bacteriological confirmation to assess the performance of smear microscopy, TB-LAMP, and Xpert assays. Both the automated liquid culture methods, such as MGIT, and solid culture methods using LJ medium were used as reference standards. While there is a marginal difference in accuracy between MGIT and LJ mediums, both culture methods are used interchangeably in clinical practice (Moreira 2015). LJ medium is more available than the automated liquid culture medium, especially in resource-limited settings. Hence, for practical reasons, a positive result of either MGIT or LJ alone or in combination was accepted as a diagnosis of tuberculosis; a negative culture indicated no tuberculosis.

Although the WHO recommends using mWRD for diagnosing tuberculosis in children, given its good sensitivity and specificity, culture is still considered a good reference standard, even for tuberculosis in children. First, culture can be used for species identification and also for drug-susceptibility testing and genotyping. Second, culture detects live bacteria, whereas Xpert assays detect both live and dead bacteria, which can increase the false-positivity rate. Finally, we anticipated most of the authors of primary studies would have used culture or clinical reference standards as the uptake of molecular diagnostic tests was low in highly endemic countries.

2. Composite reference standard

We considered a composite reference standard (CRS) as one of the reference standards. A CRS is typically defined by primary study authors, and so we accepted study-specific definitions. A CRS may include results from microbiological tests (excluding the index test), imaging, histopathology, and relevant clinical characteristics, including clinical scoring. A case was considered positive if at least one component test yielded a positive result, according to the study's predefined criteria. The diagnosis of pulmonary tuberculosis was defined as either a positive culture or a clinical decision to initiate treatment based on clinical features (i.e. clinically diagnosed tuberculosis), such as a cough lasting more than two weeks, fever, weight loss, pneumonia unresponsive to antibiotics, or a history of close contact with an adult who had tuberculosis (Kay 2022). Clinical scoring systems have been standardised since the expert consensus recommendations in 2012 (Cuevas 2012; Graham 2012; Graham 2015). For older definitions, tuberculosis was deemed 'confirmed, probable, or possible' and non-tuberculosis as 'unlikely or not tuberculosis' (Graham 2012). For newer definitions, tuberculosis was deemed 'confirmed or unconfirmed' and non-tuberculosis as 'unlikely' (Graham 2015). In line with WHO recommendations, we considered a clinical score of ≥ 10 as positive for tuberculosis (WHO 2022a; WHO 2020) (Table 1).

Search methods for identification of studies

Electronic searches

The Cochrane Infectious Diseases Group Information Specialist (Vittoria Lutje (VL)) searched the following databases on the dates indicated below, using the search terms and strategy described in Appendix 1.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 10) published in the Cochrane Library (October 2023)
- MEDLINE (Ovid, from 1946 to 2 October 2023)
- Embase (Ovid, from 1947 to 2 October 2023)
- Web of Science (Clarivate): Science Citation Index-Expanded (1900 to 2 October 2023)
- Biosis reviews (1926 to 2 October 2023)
- Scopus (Elsevier, from 1970 to 2 October 2023)
- WHO Global Index Medicus (2 October 2023)
- ProQuest Dissertations and Theses A&I (2 October 2023)

We also searched the WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch) and ClinicalTrials.gov (clinicaltrials.gov/ct2/home) for trials in progress on 2 October 2023.

Searching other resources

We examined the reference lists of included articles and relevant review articles identified through electronic searches. We searched for information on ongoing and unpublished studies from experts working on new diagnostics for tuberculosis, such as the STOP TB Partnership's New Diagnostic Working Group and FIND (the global alliance for diagnostics). A WHO public call was made between 30 November 2023 and 15 February 2024 for ongoing and unpublished studies from manufacturers and researchers. We also contacted the authors of the studies that included both adults and children for disaggregated data and additional information regarding the studies.

Data collection and analysis

We followed the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Deeks 2022).

Selection of studies

We uploaded titles and abstracts retrieved after the electronic literature search to EndNote software to remove duplicates. Subsequently, we uploaded records to Rayyan, an intelligent, systematic review software. Four review authors in pairs (MKS and TE, VA and AB) independently screened the titles and abstracts based on the eligibility criteria and marked those potentially eligible. The same author teams (MKS and TE, VA and AB) obtained and assessed the full-text articles. We also reviewed the bibliographies of the shortlisted articles for articles missed in the electronic searches. If there were any discrepancies between the review authors, a fifth review author (JD) aided in resolving the disagreement. We listed the reasons for exclusion in the 'Characteristics of excluded studies' table. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

Six review authors in three pairs (MKS and TE, VA and AB, BD and JD) independently and in duplicate extracted data using a predesigned piloted data collection form (Appendix 2), and a seventh review author (LR) resolved any disagreements.

We collected the following information from the studies and included details in the 'Characteristics of included studies' table.

1. **Study details:** first author; publication year; country where the study was performed; economic classification of the country according to the World Bank (2021 to 2022) (World Bank 2023); study setting (outpatient or inpatient setting in peripheral health institutions, peripheral or intermediate laboratories); study design; method of participant selection; total number of children screened, enrolled, excluded, and included for data analysis; study funding. We recorded the study stage for ongoing studies (completed recruitment; completed recruitment and data cleaning; ongoing recruitment; the proportion of the target sample size recruited; completed data not yet available or published).
2. **Study participants:** history of pulmonary tuberculosis, nutritional status, HIV status, and household contact with tuberculosis; details of tuberculosis treatment after diagnosis.
3. **Target condition:** pulmonary tuberculosis.
4. **Reference standards:** the number of cultures performed for each participant, either culture results alone or composite reference standards. Solid culture (LJ), automated liquid culture (MGIT), or both. Composite reference standards include: older clinical criteria (Graham 2012), updated clinical criteria (Graham 2015), WHO clinical score, study-specific clinical criteria, or decision to treat (clinically diagnosed tuberculosis).
5. **Index tests and comparator index tests:** TB-LAMP assay. In addition, details of Xpert MTB/RIF Ultra and smear microscopy if compared with TB-LAMP in comparative accuracy studies.
6. **Specimen type:** number of specimens collected (one, multiple, unknown, or unclear); specimen type (expectorated sputum, induced sputum, nasopharyngeal aspirate, gastric aspirate, broncho-alveolar aspirate, stool); and specimen condition (frozen, freshly collected, or both).
7. **Outcomes:** number of TP, TN, FP, FN, and the number of missing or unavailable test results. The time to start treatment since the sputum collection date and the time to diagnose pulmonary tuberculosis since running the TB-LAMP assay were captured.
8. **Indeterminate and non-determinate results:** number of indeterminate or invalid TB-LAMP results in accordance with manufacturer's recommendations and number of non-determinate Xpert MTB/RIF Ultra results.

When data were unavailable for relevant questions from any publication and its supplementary material, we contacted the primary study authors for more information. At least two review authors reviewed the data to decide on eligibility for inclusion in the review. We extracted the data and recorded it in Microsoft Excel, and entered it into Review Manager Web directly (RevMan Web 2022).

Assessment of methodological quality

Six review authors in three pairs (MKS and TE, VA and AB, BD and JD) independently performed the methodological quality assessment of included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting 2011). A seventh review author (LR) resolved any disagreements. In addition, we used the Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool for comparative accuracy studies of TB-LAMP versus Xpert MTB/RIF Ultra or versus smear microscopy (Yang 2021). Two review authors (JD and LR) modified, piloted, and refined those tools for our review question (see Appendix 3). We summarised the QUADAS-2 and QUADAS-C assessments graphically and narratively.

Statistical analysis and data synthesis

We performed the analyses using participants rather than specimens as the unit of analysis. We also performed analyses separately for each type of specimen, such as sputum, gastric, and nasopharyngeal aspirates, and reference standard (culture was the primary reference standard). If the primary authors reported specimen-wise analysis only, we contacted the authors to obtain participant-wise data. We estimated the sensitivity and specificity of each study with a 95% CI and graphically presented data on forest plots. We did not perform a meta-analysis due to the paucity of data. We planned to perform meta-analysis using a bivariate model to estimate summary sensitivity and specificity. None of the included studies reported non-determinate or indeterminate index test results.

Investigations of heterogeneity

We could not investigate potential sources of heterogeneity by smear status, setting, and tuberculosis burden due to paucity of data.

Sensitivity analyses

We did not perform sensitivity analyses due to the paucity of data.

Assessment of certainty of evidence

We assessed and reported the certainty of the evidence using the GRADE approach for diagnostic studies (Balshem 2011; Schünemann 2008; Schünemann 2016). We used the GRADEpro GDT online software tool (GRADEpro GDT). Our evaluation of the certainty of evidence reflected the degree to which we were confident that the estimates of sensitivity and specificity were correct. As per GRADEpro GDT, we rated the certainty of the evidence as high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) for each of the five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias.

If there were high-quality studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty, we marked the certainty of the evidence as high for both sensitivity and specificity. If there was a reason for downgrading, we used our best judgement to determine whether the reason was serious (which would result in a downgrade of one level) or very serious (which would result in a downgrade of two levels). Two review authors (LR and JD) discussed the judgements of certainty of the evidence and applied GRADE in the following format (GRADEpro GDT; Schünemann 2020a; Schünemann 2020b).

1. Risk of bias

We used QUADAS-2 and QUADAS-C tools to assess the risk of bias.

2. Indirectness

We assessed indirectness in relation to the target population (including disease spectrum), setting, index and comparator index tests, reference standards, and accuracy outcomes. We checked whether the study's population matched our review question's population of interest. We also used the prevalence of tuberculosis

given by the WHO as a guide to check whether there was indirectness in the population.

3. Inconsistency

Inconsistency could be caused by clinical or methodological heterogeneity or, sometimes, it cannot be explained. GRADE recommends downgrading for unexplained inconsistency in sensitivity and specificity estimates.

4. Imprecision

We believe that a precise estimate will allow for a clinically meaningful decision. We considered the width of the 95% CIs. We determined projected ranges for TP, FN, TN, and FP for a given prevalence of tuberculosis. We made judgements on imprecision from those calculations.

5. Publication bias

We considered the thoroughness of the literature search and contact with tuberculosis researchers, the inclusion of studies that produced precise estimates with high accuracy despite a small sample size, and knowledge about studies that were conducted but were not published while assessing publication bias.

Summary of findings

We used the GRADEpro GDT online tool to create the summary of findings tables. The summary of findings tables include the following details.

1. The review question and its components: population, setting, index test(s), and reference standard(s).
2. Summary estimates of sensitivity and specificity with 95% CIs.
3. The number of included studies and participants that contributed to the estimates of sensitivity and specificity.
4. Different estimates of the prevalence of the target condition with an explanation of why the prevalence was chosen.
5. An assessment of the certainty of the evidence (GRADE).
6. Explanations for downgrading, as required.

RESULTS

Results of the search

We identified 2806 research articles from searches of electronic sources and seven through other sources. We screened the titles and abstracts of 1138 unique articles. Of the 1138 articles, we excluded 988. We assessed the full text of 151 articles and subsequently included four studies. Figure 2 shows the flow of studies through the screening and selection process, and the Excluded studies section describes the reason for exclusion.

Figure 2. PRISMA flow diagram

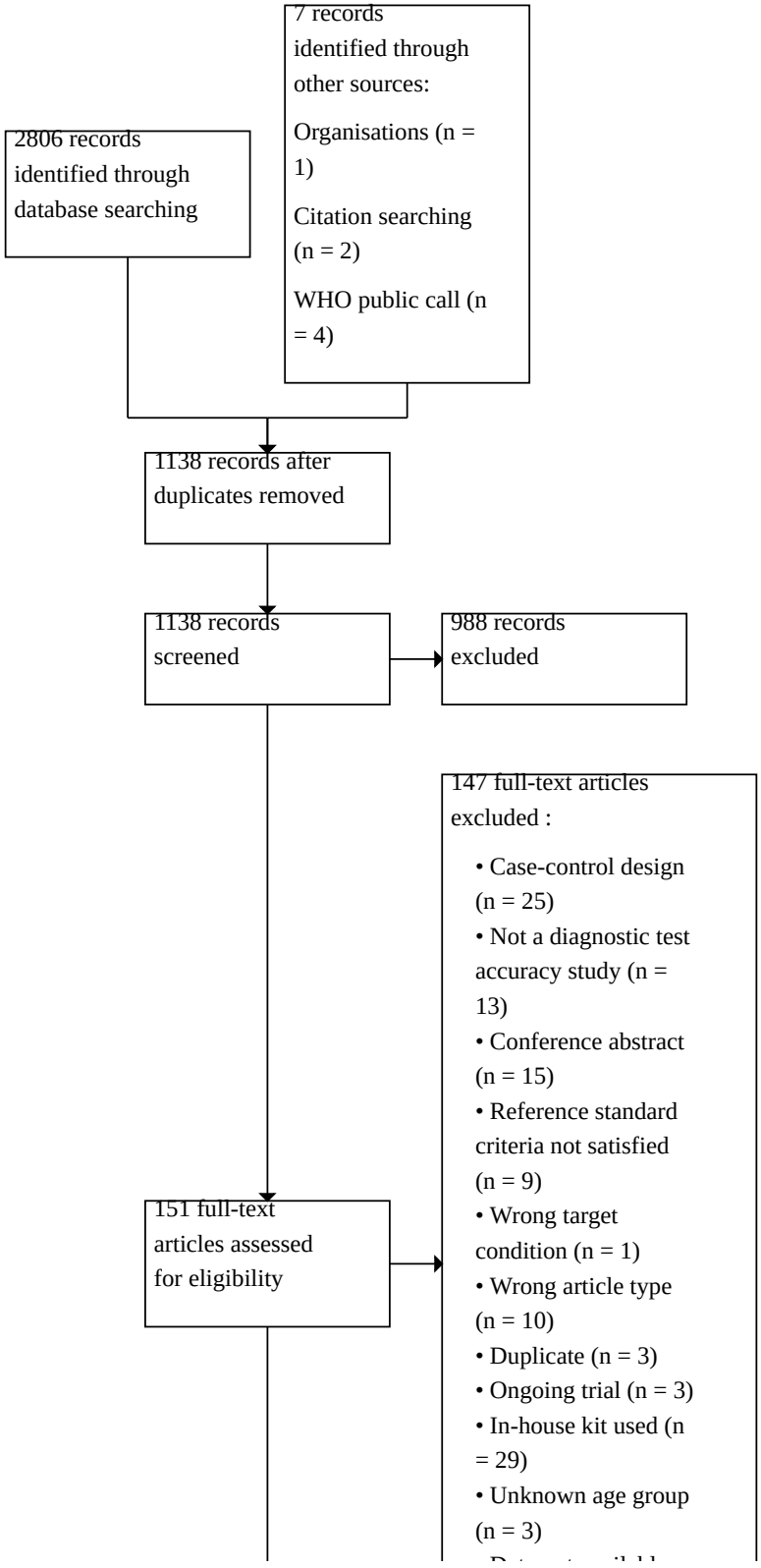
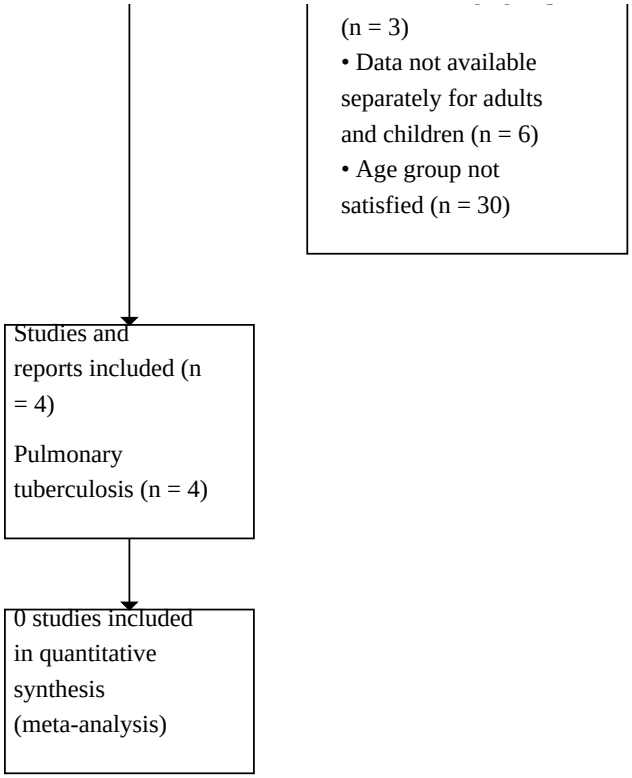


Figure 2. (Continued)



Description of included studies

All four included studies were cross-sectional studies. Bojang 2016, Donfack 2024, and Yadav 2021 were conducted in the Gambia, Cameroon, and India, which are low- and middle-income countries. One study was conducted in Thailand (Promsena 2022). Two studies were from countries with a high tuberculosis and HIV-TB burden (Promsena 2022; Yadav 2021), and one was conducted in a setting with a high multi-drug-resistant tuberculosis burden (Yadav 2021). Only one study reported participants with HIV infection (29.9%) (Donfack 2024).

Three studies used liquid culture MGIT-960 as the reference standard, while one used both solid and liquid culture (Promsena 2022). All four studies tested their samples in central labs. One study used Xpert Ultra as a comparator test (Promsena 2022), and three studies used an acid-fast stain (AFB) smear as a comparator test (Bojang 2016; Promsena 2022; Yadav 2021). Donfack 2024 only evaluated TB-LAMP.

Three studies used fresh specimens (Bojang 2016; Promsena 2022; Yadav 2021), and one study used frozen samples (Donfack 2024). Of the three studies that evaluated sputum specimens, two studies used expectorated sputum (Bojang 2016; Promsena 2022), and one study used induced sputum (Yadav 2021). Two studies used gastric lavage, gastric aspirate, and bronchoalveolar lavage (Yadav 2021; Promsena 2022); two studies used nasopharyngeal aspirates (Promsena 2022; Donfack 2024); one study used tracheal aspirate (Promsena 2022); and one study used stool specimens (Donfack 2024). Donfack 2024 evaluated TB-LAMP in nasopharyngeal aspirate, gastric aspirate, and stool in a single cohort of children.

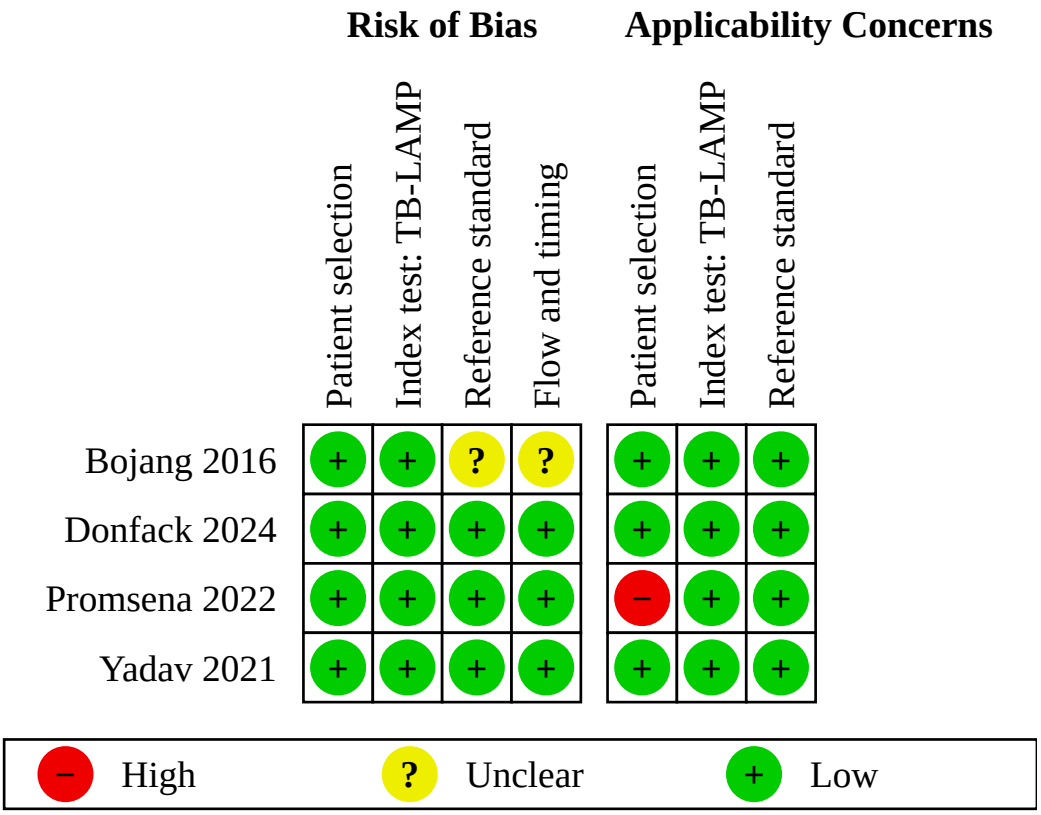
All four studies evaluated the index tests against a microbiological reference standard, and none of the included studies evaluated the index test against a composite reference standard. Key characteristics of the included studies are described in Characteristics of included studies and Table 2.

We contacted the authors of all four studies. Bojang 2016, Donfack 2024, and Yadav 2021 shared the raw data from their primary studies. Promsena 2022 provided the missing information required for the 2 x 2 table.

Methodological quality of included studies

Figure 3 summarises the results of the risk of bias and applicability assessment for each of the included studies. Methodological quality assessment data are available from the corresponding author upon request.

Figure 3. Risk of bias and applicability concerns for each included study of TB-LAMP for the diagnosis of pulmonary tuberculosis in children



Patient selection

We judged all four studies to have a low risk of bias because they enrolled the study participants randomly or consecutively and did not make any inappropriate exclusions. Three studies that evaluated comparator index tests (smear microscopy and Xpert MTB/RIF Ultra) also had a low risk of bias in the patient selection QUADAS-C domain. We judged Promsena 2022 to have high applicability concerns as children were recruited from an inpatient setting in a tertiary care hospital.

Index test

All studies were at low risk of bias since test results were machine-generated and followed pre-specified manufacturer-recommended methods. We also judged the risk of bias as low for QUADAS-C. All studies had low applicability concerns.

Reference standard

We judged one study as having an unclear risk of bias due to a lack of information about blinding in both QUADAS-2 and QUADAS-C (Bojang 2016). The remaining studies were at low risk of bias as the study personnel were blinded when interpreting the reference standard, and all used standard culture methods. We also judged them to have a low risk of bias for QUADAS-C. We assessed all studies as having low applicability concerns since mycobacterium speciation and sensitivity of the culture isolate were performed in all studies.

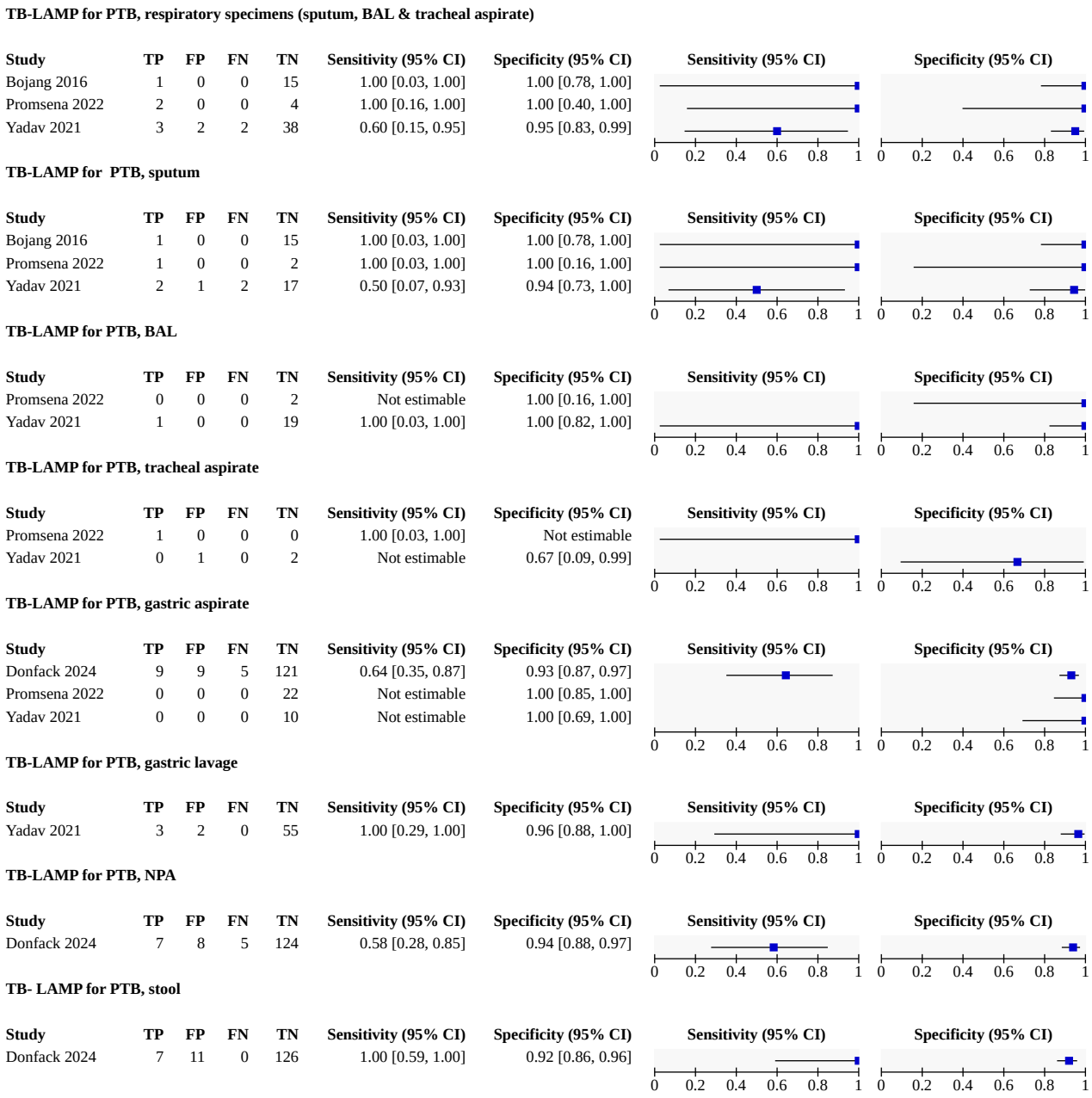
Flow and timing

We judged one study (25%) to have an unclear risk of bias for both QUADAS-2 and QUADAS-C due to a lack of clarity about the number of patients recruited and analysed (Bojang 2016). We judged the remaining studies to have a low risk of bias in both assessments.

Findings

Figure 4 summarises the sensitivity and specificity of the studies included across and for each specimen type. Four studies (303 participants and 25 children with pulmonary tuberculosis) assessed diagnostic accuracy using different specimen types. The sensitivities were between 50% and 100%, and the specificities were between 67% and 100%. Given the mix of specimen types and paucity of data, we did not perform a meta-analysis to combine results across studies. All studies evaluated diagnostic accuracy against a microbiological reference standard; none used a composite reference standard.

Figure 4. Forest plot of the accuracy of TB-LAMP in children using respiratory specimens (sputum, bronchoalveolar lavage, tracheal aspirate).
Abbreviations: BAL: bronchoalveolar lavage; FN: false negative; FP: false positive; NPA: nasopharyngeal aspirate; PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TN: true negative; TP: true positive



The sensitivities and specificities ranged from 50% to 100% and 94% to 100%, respectively, for sputum samples (3 studies, 41 participants) (Bojang 2016; Promsena 2022; Yadav 2021). Two studies (22 participants, including one with pulmonary tuberculosis) evaluated bronchoalveolar lavage (BAL). Sensitivity was not estimable for Promsena 2022, and Yadav 2021 reported a sensitivity of 100% (95% CI 3 to 100); both studies reported 100% specificities. Two studies evaluated tracheal aspirate (four participants, including one with pulmonary tuberculosis). Sensitivity was not estimable for one study (Yadav 2021), and the other study reported a sensitivity of 100% (95% CI 3 to 100) (Promsena 2022). Similarly, specificity was not estimable for Promsena 2022, and Yadav 2021 reported a specificity of 67% (95% CI 9 to 99). Overall, three studies assessed the accuracy of LC-mNAATs for detecting pulmonary tuberculosis using respiratory samples (sputum, BAL, and tracheal aspirate) (Bojang 2016; Promsena 2022; Yadav 2021). The sensitivities were between 60% and 100%, and the specificities were between 95% and 100% (67

participants, including eight with pulmonary tuberculosis); very low-certainty (sensitivity) and low-certainty (specificity) evidence (Summary of findings 1).

Three studies (176 participants, including 14 children with pulmonary tuberculosis) assessed the diagnostic accuracy for detecting pulmonary tuberculosis using gastric aspirate (Donfack 2024; Promsena 2022; Yadav 2021). Sensitivity was not estimable in two studies and was 64% in the third study. The specificities were between 93% and 100%. Yadav 2021 (60 participants, including three with pulmonary tuberculosis) evaluated pulmonary tuberculosis using gastric lavage. The sensitivity was 100% (95% CI 29 to 100), and the specificity was 96% (95% CI 88 to 100). One study (144 participants, 12 children with pulmonary tuberculosis) assessed diagnostic accuracy using nasopharyngeal aspirate (Donfack 2024). The sensitivity was 58% (95% CI 28 to 85), and the specificity was 94% (95% CI 88 to 97).

Donfack 2024 also used stool specimens for the detection of pulmonary tuberculosis. The sensitivity was 100% (95% CI 59 to 100), and the specificity was 92% (95% CI 86 to 96) (144 participants, seven children with pulmonary tuberculosis); very low-certainty (sensitivity) and low-certainty (specificity) evidence (Summary of findings 2). Donfack 2024 provided data on diagnostic accuracy in children living with HIV. The sensitivity ranged from 58% to 100% and specificity from 91% to 100% across gastric aspirate, nasopharyngeal aspirate, and stool specimens. Additional forest plots for TB-LAMP showing results by HIV status and age group are shown in Appendix 4. A forest plot showing results for TB-LAMP, Xpert Ultra, and smear microscopy is also included in Appendix 4.

Promsena 2022 reported the results of Xpert Ultra and three other studies that evaluated smear microscopy (Bojang 2016; Donfack 2024; Yadav 2021). The number of studies and the number of participants in each study are too small for a meaningful comparison of the accuracy of the tests.

DISCUSSION

In this review, we identified four studies that met our inclusion criteria. We excluded 147 studies, the most common reasons being variations in the index test due to the use of in-house kits and case-control study designs.

Summary of main results

Of the four included studies, three had a low risk of bias in all the domains, while we judged Bojang 2016 to have an unclear risk of bias in the reference standard and flow and timing domain. One study had high applicability concerns in the patient selection domain (Promsena 2022).

For the detection of pulmonary tuberculosis in respiratory samples, LC-mNAATs sensitivities were between 50% and 100%, and the specificities were between 67% and 100% (3 studies, 62 participants, 8 cases; very low-certainty (sensitivity) and low-certainty (specificity) evidence) (Summary of findings 1). The sensitivity and specificity were 100% (95% CI 29 to 100) and 96% (95% CI 88 to 100) for detection in gastric aspirate from one study (60 participants, 3 cases). For detection in nasopharyngeal aspirate, the sensitivity was 58% (95% CI 28 to 85) and the specificity was 94% (95% CI 88 to 97) (1 study, 144 participants, 12 cases). For the detection of pulmonary tuberculosis using stool samples, the sensitivity and specificity were 100% (95% CI 59 to 100) and 92% (95% CI 86 to 96), respectively (144 participants, 7 cases; very low-certainty (sensitivity) and low-certainty (specificity) evidence) (Summary of findings 2). We did not perform a meta-analysis due to limited data. One study evaluated Xpert MTB/RIF Ultra, and three studies reported the accuracy of smear microscopy. The number of participants in each study is too small for a meaningful comparison of the accuracy of the tests. Therefore, we did not fulfil our secondary objectives.

Interpretation of the results

Respiratory samples

For every 1000 children tested, if 100 had tuberculosis according to culture, 60 to 100 with tuberculosis would be identified as positive by the TB-LAMP test. Of the 900 children without tuberculosis, 855 to 900 would be identified as negative by the test.

Gastric aspirate

For every 1000 children tested, if 100 had tuberculosis according to culture, 64 with tuberculosis would be identified as positive by the TB-LAMP test. Of the 900 children without tuberculosis, 837 to 900 would be identified as negative by the test.

Gastric lavage

For every 1000 children tested, if 100 had tuberculosis according to culture, 135 would be TB-LAMP positive, of which 100 would have tuberculosis (true positives), and 35 would not have tuberculosis (false positives); 865 would be TB-LAMP negative, of which 864 would not have tuberculosis (true negatives), and one would have tuberculosis (false negative).

Nasopharyngeal aspirate

For every 1000 children tested, if 100 had tuberculosis according to culture, 112 would be TB-LAMP positive, of which 58 would have tuberculosis (true positives), and 54 would not have tuberculosis (false positives); 888 would be test-negative, of which 846 would not have tuberculosis (true negatives), and 42 would have tuberculosis (false negatives).

Stool

For every 1000 children tested, if 100 had tuberculosis according to culture, 171 would be TB-LAMP positive, of which 99 would have tuberculosis (true positives), and 72 would not have tuberculosis (false positives); 829 would test negative, of which 828 would not have tuberculosis (true negatives) and one child would have tuberculosis (false negative).

Strengths and weaknesses of the review

Completeness of evidence

Our review used a comprehensive search strategy, and we searched several databases. We also handsearched the reference lists of included studies, and contacted tuberculosis experts for missing studies. We received unpublished reports through the WHO public call for data. We contacted the corresponding authors for additional information before excluding the studies. We set stringent eligibility criteria and included all studies that fulfilled the criteria. We obtained data for three out of four studies from the study authors and extracted data after removing individuals above the age of 10 years. The corresponding author of Promsena 2022 provided the

missing information required for the 2 x 2 table. The authors of the other included studies provided the raw data from which we extracted the required information. We also excluded studies that used in-house assays. We believe the chance that we may have missed relevant studies to be minimal.

We could not perform a meta-analysis to fulfil our secondary objectives of comparing the test accuracies due to limited data.

Accuracy of the reference standards used

In our review, we decided to include two reference standards, culture and a composite reference standard, because culture is not the best way to determine disease status in children due to the paucibacillary nature of tuberculosis. A composite reference standard is expected to overcome this deficiency by incorporating a set of clinical criteria. However, none of our included studies used a composite reference standard. All four included studies used either an MGIT medium or an Ogawa solid culture method.

Quality assessment and quality of reporting of the included studies

Overall, the risk of bias was low. Except for Bojang 2016, we judged all studies to have a low risk of bias for the patient selection, index test, reference standard, and flow timing domains. Bojang 2016 did not sufficiently explain the blinding and patient recruitment processes. Promsena 2022 recruited patients from an inpatient setting and hence had high applicability concerns.

Comparison with other systematic reviews

To our knowledge, there is no published review on the accuracy of TB-LAMP for detecting pulmonary tuberculosis in children. According to the systematic review by Shete et al, the summary sensitivity of TB-LAMP was 78% to 80% (based on the number of culture reference standards used), and the summary specificity was 98% for sputum-positive tuberculosis in adults (Shete 2019). WHO policy guidance (2016) included 13 studies. The sensitivity of TB-LAMP in various settings ranged between 76% and 80%, and the specificity between 97% and 98% in adults (WHO 2016b). Since very few data were available, a meaningful comparison could not be made with the available adult data. We hope to periodically update this review as more studies become available.

Applicability of findings to the review question

We judged most of the studies to have low applicability concerns. We judged Promsena 2022 to have high applicability concerns as this study recruited children from an inpatient setting at a tertiary care hospital.

AUTHORS' CONCLUSIONS

Implications for practice

Our review included very few studies that evaluated the diagnostic accuracy of low-complexity manual nucleic acid amplification tests (LC-mNAATs) for the detection of pulmonary tuberculosis and showed a very low certainty of evidence for sensitivity and low certainty of evidence for specificity. The evidence to support the use of the LC-mNAATs as an initial molecular test in children is limited.

Implications for research

Since our review demonstrated that there is limited evidence on the diagnostic accuracy of LC-mNAATs in children, we suggest the following for consideration in future studies of children.

- Well-powered studies to determine the diagnostic accuracy of LC-mNAATs for diagnosing pulmonary tuberculosis.
- Evaluation of diagnostic accuracy against a composite or clinical reference standard in children.
- Inclusion of children aged 0 to 9 years to align with the World Health Organization (WHO) age definition.
- Inclusion of more children living with HIV.
- Addressing comparative accuracy through head-to-head comparisons of the accuracy of LC-mNAATs and low-complexity automated nucleic acid amplification tests (LC-aNAATs) to understand the differences in test accuracy.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editors (final editorial decision): Karen Steingart, Honorary Research Fellow, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK (Clinical Sign-off Editor at first decision); Hellen Gelband, Senior Fellow, Centre for Global Health Research, University of Toronto (Clinical Sign-off Editor at final decision); Gianni Virgili, Department NEUROFARBA, University of Florence, Italy (Diagnostic Test Accuracy Sign-off Editor).
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Hannah Payne, Central Editorial Service.
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Jessenia Hernandez, Central Editorial Service.

- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane Central Production Service.
- Peer reviewers (provided comments and recommended an editorial decision):
  - Bryan Vonasek, Michigan State University (clinical/content review);
  - Susanna S van Wyk, Centre for Evidence-Based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University (DTA methods review);
  - Sulakshna Suri (consumer review);
  - Jo Platt, Central Editorial Information Specialist (search review);
  - Sofia Tsokani, Cochrane CET (statistical review);
  - one additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bojang 2016

Study characteristics	
Patient Sampling	Individuals with presumptive tuberculosis aged 1 year to 91 years were recruited from outpatient settings in the Gambia. Children less than 10 years of age included in this review.
Patient characteristics and setting	Study design: cross-sectional Presenting signs and symptoms: cough for more than 2 weeks, plus one other symptom such as night sweats, fever, and unintentional weight loss Age: 1 to 8 years Total recruited for the study: 441 (285 before treatment and 156 for follow-up after diagnosis). Data for children less than 10 years recruited before the treatment were obtained from the authors. No. of patients considered for analysis: 16 Gender: 7 females (50%) HIV infection: not reported History of TB: not reported Clinical setting: outpatients at the Medical Research Council unit, Fajara and peripheral health clinics Laboratory level: central Country: The Gambia World Bank Income Classification: lower-middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: no
Index tests	TB-LAMP
Target condition and reference standard(s)	Pulmonary tuberculosis. The reference standard was liquid culture (MGIT960). All the tests were done in the central lab.
Flow and timing	Sample transportation and flow of analysis are not reported.
Comparative	Smear microscopy has been used as the comparator.

Bojang 2016 *(Continued)*

Notes	Funded by FIND (Foundation for Innovative New Diagnostics)

Methodological quality

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

Bojang 2016 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Unclear		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			

Donfack 2024

Study characteristics	
Patient Sampling	Children with presumptive tuberculosis were prospectively recruited from outpatient settings in Cameroon.
Patient characteristics and setting	Study design: cross-sectional study Presenting signs and symptoms: children under 15 years were included when the clinician suspected intrathoracic TB (clinical conviction) and if at least one of the symptoms and signs of tuberculosis was present Age: 3 months to 9 years Total recruited for the study: 150 No. of patients considered for analysis: 144 (after excluding children more than or equal to 10 years of age). Individual patient data were obtained from the authors. Sex: 63 females (43.8%) HIV infection: 43 (29.9%) History of TB: not reported Clinical setting: outpatient setting Laboratory level: central Country: Cameroon World Bank Income Classification: lower-middle income High TB burden country: no High MDR-TB burden country: no High TB/HIV burden country: yes

Donfack 2024 *(Continued)*

Index tests	TB-LAMP
Target condition and reference standard(s)	Pulmonary tuberculosis. Reference standard was liquid culture (MGIT960). All the tests were done in the central lab.
Flow and timing	Decontaminated pellets from the culture were used to perform the TB-LAMP test. The culture was performed with non-treated samples. Decontaminated pellets from gastric aspiration, nasopharyngeal aspirates, and stool samples were stored at -20 °C at the National Reference Laboratory. One vial of each sample was tested using TB LAMP.
Comparative	Smear microscopy. The study also used Xpert MTB/RIF, which is not our index test of interest.
Notes	Funding support from Eiken Chemicals (Tokyo, Japan)

Methodological quality

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

Donfack 2024 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			

Promsena 2022

Study characteristics	
Patient Sampling	Children with presumptive pulmonary tuberculosis were enrolled consecutively in the study.
Patient characteristics and setting	Study design: cross-sectional study Age: children under 18 years were recruited for the study. Our review includes children less than 10 years old. Total recruited for the study: 75 children were included in the study. We requested information on children less than 10 years from the authors. No. of patients considered for analysis: 28 Gender: 12 females (42.8%) HIV infection: not reported History of TB: not reported Clinical setting: inpatient setting in tertiary care hospital Laboratory level: central Country: Thailand World Bank Income Classification: upper-middle income High TB burden country: yes High MDR-TB burden country: no

Promsena 2022 *(Continued)*

	High TB/HIV burden country: yes
Index tests	TB-LAMP
Target condition and reference standard(s)	Pulmonary tuberculosis. Reference standard was liquid culture (MGIT960) and OGAWA. All the tests were done in the central lab.
Flow and timing	The specimens were processed immediately after transfer to the laboratory or after storage at 4 °C for a maximum of 72 hours.
Comparative	Smear microscopy and Xpert MTB/RIF Ultra
Notes	Funded by Chulalongkorn University and the Health Systems Research Institute, Thailand

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index test (TB-LAMP)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index test (Smear microscopy)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Promsena 2022 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index test (Xpert MTB/RIF Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference standard			
Is the reference standard likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			

Yadav 2021

Study characteristics	
Patient Sampling	The respiratory samples from children < 15 years of age, which were received in the National Tuberculosis Elimination Programme lab for TB diagnosis, were included in the study.
Patient characteristics and setting	Study design: cross-sectional study Age: children less than 15 years old

Yadav 2021 *(Continued)*

	Total recruited for the study: 177 were included. We obtained raw data and included 115 children less than 10 years in this review. No. of patients considered for analysis: 115 Sex: 45 females (35.2%) HIV infection: not reported History of TB: not reported Clinical setting: outpatient clinics of the National Tuberculosis Elimination Programme Laboratory level: central Country: India World Bank Income Classification: lower-middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes
Index tests	TB- LAMP
Target condition and reference standard(s)	Pulmonary tuberculosis. Reference standard was liquid culture (MGIT960). All the tests were done in the central lab.
Flow and timing	The index tests and reference standards were performed in parallel.
Comparative	Smear microscopy. The study also included Xpert MTB/RIF as a comparator, which was not an index test of our interest.
Notes	Received TB-LAMP consumables from Human Diagnostics and NextGen In-Vitro Diagnostics Private Limited.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index test (TB-LAMP)			

Yadav 2021 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index test (Smear microscopy)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index test (Xpert MTB/RIF Ultra)			
DOMAIN 3: Reference standard			
Is the reference standard likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			

HIV: human immunodeficiency virus
MDR-TB: multidrug-resistant tuberculosis
TB: tuberculosis
TB-LAMP: tuberculosis loop-mediated isothermal amplification

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

Study	Reason for exclusion
Aryan 2010	Case-control study (in-house)
Aryan 2013	In-house
Aryan 2014	Conference abstract
Aryan 2016	Conference abstract
Baikunje 2019	Case-control study (in-house)
Balne 2013	Case-control atudy (in-house)
Balne 2015a	Reference standard not satisfied
Balne 2015b	Conference abstract
Benellam 2022	Reference standard not satisfied
Bentaleb 2016	In-house
Bhirud 2017	Unknown age group
Boehme 2007	Age group not satisfied
Bumbrah 2023	Wrong article type
Cao 2015	Case-control study (in-house)
Cheng 2020	Age group not satisfied
Ckumdee 2016	Wrong target condition
Dayal 2020	In-house
Deng 2019	Wrong article type
Deng 2021	Case-control study
Dolker 2012	In-house
Donfack 2018	Age group not satisfied
Donfack 2023	Age group not satisfied
Donfack 2024a	Age group not satisfied
Donfack 2024b	Age group not satisfied
Fan 2022	Data not available separately for adults and children
Fujisaki 2004	Not a DTA study

Study	Reason for exclusion
Gelaw 2017	Age group not satisfied
Geojith 2011a	Reference standard not satisfied
Geojith 2011b	In-house
Getahun 2017	Age group not satisfied
Ghosh 2017	Unknown age group
Govindan 2021	In-house
Gray 2016	Age group not satisfied
Habeenzu 2017	In-house
Habiburrahman 2021	Wrong article type
Han 2020	Age group not satisfied
Ignatov 2014	Not a DTA study
Iwamoto 2003	Not a DTA study
Jana 2019	Conference abstract
Jaroenram 2020	Not a DTA study
Jekloh 2022	In-house
Joon 2015	In-house
Joon 2017	In-house
Joon 2019	In-house
Juliasih 2020	Reference standard not satisfied
Kaewphinit 2017	In-house
Kaku 2016	Age group not satisfied
Khan 2021	Case-control study (in-house)
Khumwan 2022	Reference standard not satisfied
Kim 2018	Age group not satisfied
Kim 2023	Reference standard not satisfied
Kohan 2011	In-house
Kohan 2012	In-house
Kumar 2014	In-house

Study	Reason for exclusion
Kumar 2016	Duplicate (part of Kumar 2014)
Lee 2009	Not a DTA study
Lee 2010	Not a DTA study
Li 2014a	Not a DTA study
Li 2014b	In-house
Lin 2021	Uknown age group
Lin 2022	Data not available separately for adults and children
Ling 2008	Wrong article type
Lisdawati 2012	Not a DTA study
Liu 2022	Data not available separately for adults and children
Miller 2013	Conference abstract
Mishra 2018	Data not available separately for adults and children
Mitarai 2011	Age group not satisfied
Mitha 2020	Age group not satisfied
Modi 2016	Case-control study (in-house)
Moon 2015	In-house
Mor 2022	In-house
Mougang 2021	Ongoing trial
N'guessan 2016	Age group not satisfied
Nagai 2016a	Reference standard not satisfied
Nagai 2016b	Wrong article type
Nagdev 2011	Case-control study (in-house)
Nakiyingi 2018	Age group not satisfied
Neshani 2023	Not a DTA study
Ngando 2017	Conference abstract
Nguyen 2018	Data not available separately for adults and children
Nimesh 2014	In-house
Nischal 2019	Conference abstract

Study	Reason for exclusion
Nliwasa 2016	Age group not satisfied
Odume 2021	Age group not satisfied
Ou 2014	Age group not satisfied
Ou 2016	Age group not satisfied
Ou 2019	Age group not satisfied
Pandey 2008	Case-control study (in-house)
Perera 2018	In-house
Pham 2018	Age group not satisfied
Phetsuksiri 2019	Not a DTA study
Phetsuksiri 2020a	In-house
Phetsuksiri 2020b	In-house
Poudel 2009	Case-control study (in-house)
Promsena 2020	Ongoing trial
Rafati 2014	In-house
Rajput 2019	Data not available separately for adults and children
Rakotosamimanana 2019	Age group not satisfied
Reddy 2017	Age group not satisfied
Seki 2015	Conference abstract
Sethi 2012	Conference abstract
Sethi 2013a	In-house
Sethi 2013b	Wrong article type
Sethi 2013c	Duplicate
Sethi 2016a	In-house
Sethi 2016b	Duplicate
Sharma 2014	Case-control study (in-house)
Sharma 2015a	Wrong article type
Sharma 2015b	Case-control study (in-house)
Sharma 2016a	Case-control study (in-house)

Study	Reason for exclusion
Sharma 2016b	Case-control study (in-house)
Sharma 2019	Case-control study (in-house)
Sharma 2020a	Conference abstract
Sharma 2020b	Case-control study (in-house)
Sharma 2020c	Case-control study (in-house)
Sharma 2020d	Case-control study (in-house)
Sharma 2020e	Case-control study (in-house)
Sharma 2023	Reference standard not satisfied
Shete 2019	Wrong article type
Singh 2019a	Conference abstract
Singh 2019b	Conference abstract
Singh 2021	Age group not satisfied
Song 2021	Reference standard not satisfied
Spooner 2022	Age group not satisfied
Sreedeep 2020	In-house
Sun 2017	Case-control study (in-house)
Teramoto 2011	Conference abstract
Thapa 2019	In-house
Thomas 2022	Conference abstract
Toonkomdang 2020	In-house
Vaidya 2017	Conference abstract
Wahid 2020	Age group not satisfied
Wang 2019	Age group not satisfied
Wang 2021	Case-control study (in-house)
Wen 2023	Not a DTA study
Wu 2017	Case-control study (in-house)
Wu 2018	In-house
Xin-xin 2023	Age group not satisfied

Study	Reason for exclusion
Yadav 2017	Age group not satisfied
Yadav 2020	Case-control study
Yadav 2023	Case-control study (in-house)
Yan 2016	Wrong article type
Yang 2011	Case-control study (in-house)
Yu 2018	Wrong article type
Yuan 2014	Not a DTA study
Zhao 2017	Case-control study (in-house)
Zhu 2009	Not a DTA study

DTA: diagnostic test accuracy

D A T A

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

Table Tests. Data tables by test

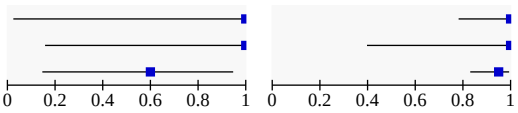
Test	No. of studies	No. of participants
1 TB-LAMP for PTB, respiratory specimens (sputum, BAL & tracheal aspirate)	3	67
2 Xpert Ultra, respiratory specimens	1	3
3 Smear microscopy, respiratory specimens	3	67
4 TB-LAMP for PTB, < 1 year, sputum	1	2
5 TB-LAMP for PTB, 1 to 4 years, sputum	2	12
6 TB-LAMP for PTB, 5 to 9 years, sputum	2	24
7 TB-LAMP for PTB, sputum	3	41
8 TB-LAMP for PTB, BAL	2	22
9 TB-LAMP for PTB, tracheal aspirate	2	4
10 TB-LAMP for PTB, gastric aspirate	3	176
11 Xpert Ultra, gastric aspirate	1	22
12 Smear microscopy, gastric aspirate	2	32

Test	No. of studies	No. of participants
13 TB-LAMP for PTB, gastric lavage	1	60
14 TB-LAMP for PTB, NPA	1	144
15 TB- LAMP for PTB, stool	1	144
16 TB-LAMP for EPTB, lymph node	1	9
17 TB- LAMP for PTB, <1 year, gastric aspirate	2	13
18 TB-LAMP for PTB, 5 to 9 years, gastric aspirate	2	48
19 TB-LAMP for PTB, 1 to 4 years, gastric aspirate	2	93
20 TB-LAMP for PTB, CLHIV, gastric aspirate	1	43
21 TB-LAMP for PTB, CLHIV, NPA	1	43
22 TB- LAMP for PTB, CLHIV, stool	1	43
23 TB-LAMP for PTB, HIV negative, gastric aspirate	1	101
24 TB-LAMP for PTB, HIV negative, NPA	1	101
25 TB-LAMP for PTB, HIV negative, stool	1	101
26 TB-LAMP for PTB, <1 year, gastric lavage	1	10
27 TB-LAMP for PTB, 1 to 4 years, gastric lavage	1	25
28 TB-LAMP for PTB, 5 to 9 years, gastric lavage	1	25
29 TB-LAMP for PTB, <1 year, NPA	1	11
30 TB-LAMP for PTB, 1 to 4 years, NPA	1	88
31 TB-LAMP for PTB, 5 to 9 years, NPA	1	45
32 TB-LAMP for PTB, <1 year, BAL	1	5
33 TB-LAMP for PTB, 1 to 4 yrs, BAL	1	9
34 TB-LAMP for PTB, 5 to 9 years, BAL	1	6
35 TB-LAMP for PTB, <1 year, stool	1	11
36 TB-LAMP for PTB, 1 to 4 years, stool	1	88
37 TB-LAMP for PTB, 5 to 9 years, stool	1	45
38 TB- LAMP for PTB, smear positive, respiratory specimens	1	2
39 TB- LAMP for PTB, smear negative, respiratory specimens	3	63
40 TB- LAMP for PTB, smear negative, gastric aspirate	1	10

Test	No. of studies	No. of participants
41 TB- LAMP for PTB, smear negative, gastric lavage	1	60
42 Smear microscopy, gastric lavage	1	60

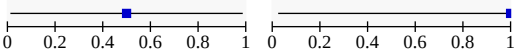
Test 1. TB-LAMP for PTB, respiratory specimens (sputum, BAL & tracheal aspirate)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]		
Promsena 2022	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]		
Yadav 2021	3	2	2	38	0.60 [0.15, 0.95]	0.95 [0.83, 0.99]		



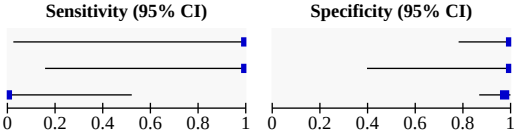
Test 2. Xpert Ultra, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	1	0	1	1	0.50 [0.01, 0.99]	1.00 [0.03, 1.00]		



Test 3. Smear microscopy, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]		
Promsena 2022	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]		
Yadav 2021	0	1	5	39	0.00 [0.00, 0.52]	0.97 [0.87, 1.00]		

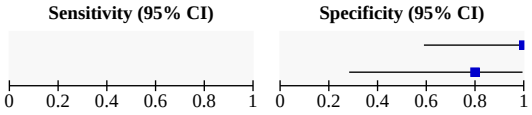


Test 4. TB-LAMP for PTB, < 1 year, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	2	Not estimable	1.00 [0.16, 1.00]		

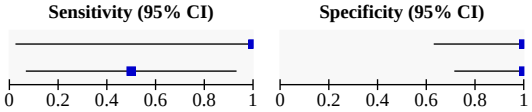
Test 5. TB-LAMP for PTB, 1 to 4 years, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]		
Yadav 2021	0	1	0	4	Not estimable	0.80 [0.28, 0.99]		



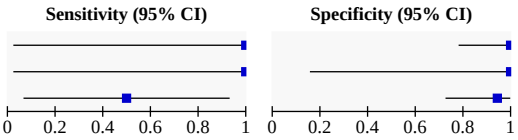
Test 6. TB-LAMP for PTB, 5 to 9 years, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	8	1.00 [0.03, 1.00]	1.00 [0.63, 1.00]		
Yadav 2021	2	0	2	11	0.50 [0.07, 0.93]	1.00 [0.72, 1.00]		



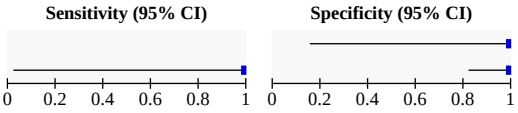
Test 7. TB-LAMP for PTB, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]
Promsena 2022	1	0	0	2	1.00 [0.03, 1.00]	1.00 [0.16, 1.00]
Yadav 2021	2	1	2	17	0.50 [0.07, 0.93]	0.94 [0.73, 1.00]



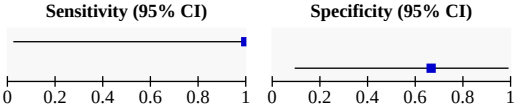
Test 8. TB-LAMP for PTB, BAL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	0	0	0	2	Not estimable	1.00 [0.16, 1.00]
Yadav 2021	1	0	0	19	1.00 [0.03, 1.00]	1.00 [0.82, 1.00]



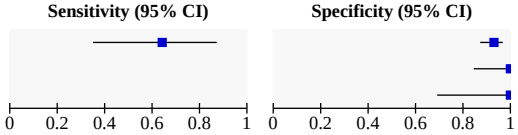
Test 9. TB-LAMP for PTB, tracheal aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Yadav 2021	0	1	0	2	Not estimable	0.67 [0.09, 0.99]



Test 10. TB-LAMP for PTB, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	9	9	5	121	0.64 [0.35, 0.87]	0.93 [0.87, 0.97]
Promsena 2022	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]

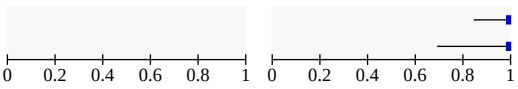


Test 11. Xpert Ultra, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	0	1	0	21	Not estimable	0.95 [0.77, 1.00]

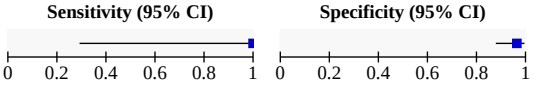
Test 12. Smear microscopy, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]



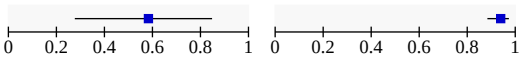
Test 13. TB-LAMP for PTB, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	3	2	0	55	1.00 [0.29, 1.00]	0.96 [0.88, 1.00]



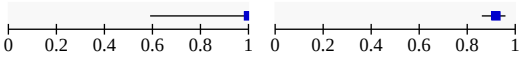
Test 14. TB-LAMP for PTB, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	8	5	124	0.58 [0.28, 0.85]	0.94 [0.88, 0.97]		



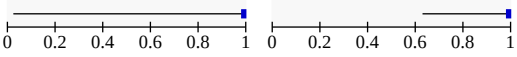
Test 15. TB- LAMP for PTB, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	11	0	126	1.00 [0.59, 1.00]	0.92 [0.86, 0.96]		



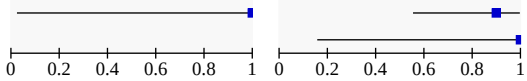
Test 16. TB-LAMP for EPTB, lymph node

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	1	0	0	8	1.00 [0.03, 1.00]	1.00 [0.63, 1.00]		



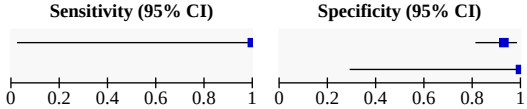
Test 17. TB- LAMP for PTB, <1 year, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	1	0	9	1.00 [0.03, 1.00]	0.90 [0.55, 1.00]		
Yadav 2021	0	0	0	2	Not estimable	1.00 [0.16, 1.00]		



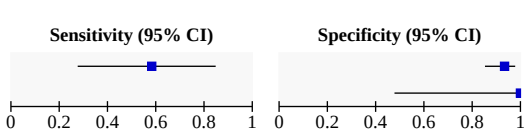
Test 18. TB-LAMP for PTB, 5 to 9 years, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	3	0	41	1.00 [0.03, 1.00]	0.93 [0.81, 0.99]		
Yadav 2021	0	0	0	3	Not estimable	1.00 [0.29, 1.00]		



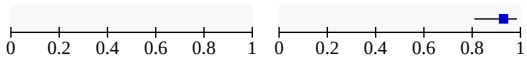
Test 19. TB-LAMP for PTB, 1 to 4 years, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	5	5	71	0.58 [0.28, 0.85]	0.93 [0.85, 0.98]		
Yadav 2021	0	0	0	5	Not estimable	1.00 [0.48, 1.00]		



Test 20. TB-LAMP for PTB, CLHIV, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	0	3	0	40	Not estimable	0.93 [0.81, 0.99]		



Test 21. TB-LAMP for PTB, CLHIV, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	0	0	0	43	Not estimable	1.00 [0.92, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 22. TB- LAMP for PTB, CLHIV, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	0	3	0	40	Not estimable	0.93 [0.81, 0.99]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 23. TB-LAMP for PTB, HIV negative, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	9	6	5	81	0.64 [0.35, 0.87]	0.93 [0.86, 0.97]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 24. TB-LAMP for PTB, HIV negative, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	8	5	81	0.58 [0.28, 0.85]	0.91 [0.83, 0.96]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 25. TB-LAMP for PTB, HIV negative, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	8	0	86	1.00 [0.59, 1.00]	0.91 [0.84, 0.96]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 26. TB-LAMP for PTB, <1 year, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 27. TB-LAMP for PTB, 1 to 4 years, gastric lavage

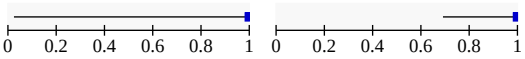
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	2	1	0	22	1.00 [0.16, 1.00]	0.96 [0.78, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Test 28. TB-LAMP for PTB, 5 to 9 years, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	23	1	0	1	1.00 [0.85, 1.00]	0.50 [0.01, 0.99]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

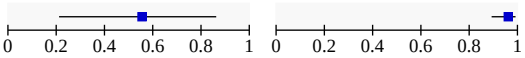
Test 29. TB-LAMP for PTB, <1 year, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	0	0	10	1.00 [0.03, 1.00]	1.00 [0.69, 1.00]		



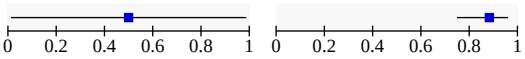
Test 30. TB-LAMP for PTB, 1 to 4 years, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	5	3	4	76	0.56 [0.21, 0.86]	0.96 [0.89, 0.99]		



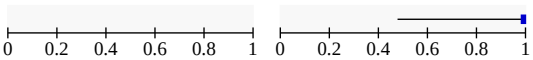
Test 31. TB-LAMP for PTB, 5 to 9 years, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	5	1	38	0.50 [0.01, 0.99]	0.88 [0.75, 0.96]		



Test 32. TB-LAMP for PTB, <1 year, BAL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	5	Not estimable	1.00 [0.48, 1.00]		

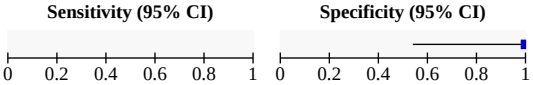


Test 33. TB-LAMP for PTB, 1 to 4 yrs, BAL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	1	0	0	8	1.00 [0.03, 1.00]	1.00 [0.63, 1.00]		

Test 34. TB-LAMP for PTB, 5 to 9 years, BAL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	6	Not estimable	1.00 [0.54, 1.00]		

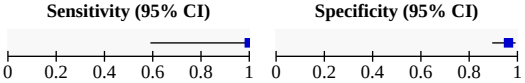


Test 35. TB-LAMP for PTB, <1 year, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	0	3	0	8	Not estimable	0.73 [0.39, 0.94]		

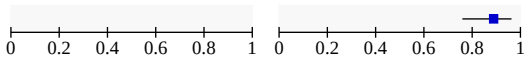
Test 36. TB-LAMP for PTB, 1 to 4 years, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	3	0	78	1.00 [0.59, 1.00]	0.96 [0.90, 0.99]		



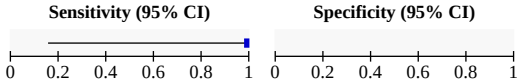
Test 37. TB-LAMP for PTB, 5 to 9 years, stool

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	0	5	0	40	Not estimable	0.89 [0.76, 0.96]		



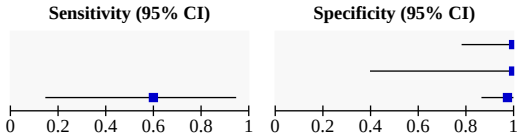
Test 38. TB- LAMP for PTB, smear positive, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	2	0	0	0	1.00 [0.16, 1.00]	Not estimable		



Test 39. TB- LAMP for PTB, smear negative, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	0	0	0	15	Not estimable	1.00 [0.78, 1.00]		
Promsena 2022	0	0	0	4	Not estimable	1.00 [0.40, 1.00]		
Yadav 2021	3	1	2	38	0.60 [0.15, 0.95]	0.97 [0.87, 1.00]		

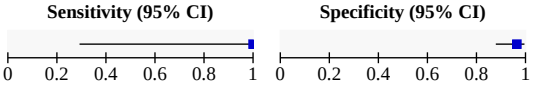


Test 40. TB- LAMP for PTB, smear negative, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]		

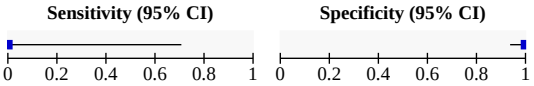
Test 41. TB- LAMP for PTB, smear negative, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	3	2	0	55	1.00 [0.29, 1.00]	0.96 [0.88, 1.00]		



Test 42. Smear microscopy, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	3	57	0.00 [0.00, 0.71]	1.00 [0.94, 1.00]		



ADDITIONAL TABLES

Table 1. Clinical score for the diagnosis of tuberculosis in children

No.	Clinical symptoms and signs	Score when chest x-ray is available	Score when chest x-ray is not available
Patient history			
1	Fever lasting > 2 weeks	5	10

Table 1. Clinical score for the diagnosis of tuberculosis in children *(Continued)*

2	Cough lasting > 2 weeks	2	5
3	Haemoptysis	4	9
4	Weight loss	3	5
5	Lethargy	3	4
6	Night sweats	2	6
Physical examination			
7	Enlarged lymph nodes	4	7
8	Tachycardia	2	4
9	Tachypnoea	1	2
Chest X-ray			
10	Enlarged lymph nodes	17	—
11	Miliary patterns	15	—
12	Pleural effusion	8	—
13	Cavitary lesion	6	—
14	Opacities	5	—
Total score[a]		77	52

[a]A total score of 10 or greater requires initiation of treatment for tuberculosis (adopted from WHO 2022b).

Table 2. Key characteristics of included studies

Study	Country	Reference standard	Clinical setting	Type of specimen	HIV status	Number of participants	Type of report
Bojang 2016	Gambia	MGIT	Outpatient	Expectorated sputum	Not reported	16	Published
Donfack 2024	Cameroon	MGIT	Outpatient	Gastric aspirate, nasopharyngeal aspirate, stool	43 (30%)	144	Unpublished
Promsena 2022*	Thailand	MGIT and Ogawa	Inpatient	Expectorated sputum, induced sputum, BAL, gastric lavage, nasopharyngeal aspirate, and tracheal aspirate	Not reported	28	Published
Yadav 2021	India	MGIT	Not reported	Probably induced sputum, gastric aspirate, gastric lavage, and BAL	Not reported	115	Published

*Evaluated both pulmonary and extrapulmonary tuberculosis.
BAL = bronchoalveolar lavage; MGIT = mycobacteria growth indicator tube
Notes: All authors were contacted for additional data or information. Bojang 2016 was funded by FIND (Foundation for Innovative New Diagnostics). Promsena 2022 received funding from Chulalongkorn University and the Health Systems Research Institute, Thailand. The authors of Yadav 2021 received TB-LAMP consumables from Human Diagnostics and NextGen In-Vitro Diagnostics private limited. Donfack 2024 received funding support from Eiken Chemicals (Tokyo, Japan).

APPENDICES

Appendix 1. Detailed search strategies

Ovid MEDLINE(R) ALL <1946 to September 29, 2023>

1 Mycobacterium tuberculosis/

2 Tuberculosis, Pulmonary/

3 Extensively Drug-Resistant Tuberculosis/

4 Tuberculosis, Multidrug-Resistant/

5 (tuberculosis or TB).tw.

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

7 exp Tuberculosis, Extrapulmonary/

8 5 and 6

9 7 or 8

10 1 or 2 or 3 or 4 or 9

11 TB-LAMP*.mp.

12 Loop-Mediated Isothermal Amplification.mp.

13 LAMP.mp.

14 LOOPAMP*.mp.

15 12 or 13 or 14

16 10 and 15

17 11 or 16

Embase 1947-Present, updated daily

1 Mycobacterium tuberculosis/

2 Lung tuberculosis/

3 extensively drug resistant tuberculosis/

4 drug resistant tuberculosis/

5 (tuberculosis or TB).tw.

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

7 extrapulmonary tuberculosis/

8 5 and 6

9 7 or 8

10 1 or 2 or 3 or 4 or 9

11 TB-LAMP*.mp.

12 Loop-Mediated Isothermal Amplification.mp.

13 LAMP.mp.

14 LOOPAMP*.mp.

15 12 or 13 or 14

16 10 and 15

17 11 or 16

Web of Science Search Strategy (Science Citation index-Expanded and Biosis previews)

#1 Search: tuberculosis or TB (Topic)

#2 Search: (extrapulmonary or lymph node* or mening* or pulmonary or lung) (Topic)

#3 Search: multidrug resistant tuberculosis or extensively drug resistant tuberculosis (Topic)

#4 Search: MDR-TB or XDR-TB (Topic)

#5 Search: #1 AND #2

#6 Search: #3 OR #4 OR #5

#7 Search: Loop-Mediated Isothermal Amplification (Topic)

#8 Search: TB-LAMP* or LOOPAMP* (Topic)

#9 Search: #7 OR #8

#10 Search: #6 AND #9

Scopus Elsevier

((TITLE-ABS-KEY (loop-mediated AND isothermal AND amplification)) OR (TITLE-ABS-KEY (loop AND mediated AND isothermal AND amplification)) OR (TITLE-ABS-KEY (tb-lamp* OR loopamp*))) AND ((TITLE-ABS-KEY ((tuberculosis OR tb) AND (extrapulmonary OR lymph AND node* OR mening* OR pulmonary))) OR (TITLE-ABS-KEY ((multidrug AND resistant AND tuberculosis) OR (extensively AND drug AND resistant AND tuberculosis))) OR (TITLE-ABS-KEY (mdr-tb OR xdr-tb)))

ProQuest Dissertations & Theses A&I

Tuberculosis and Loop-Mediated Isothermal Amplification and (diagnos* or detect* or assay*) OR TB-LAMP

Search Name: Cochrane Central Register of Controlled Trials

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#1 MeSH descriptor: [Tuberculosis] explode all trees

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

#3 ((tuberculosis or TB or MDR-TB or XDR-TB)):ti,ab,kw

#4 extrapulmonary tuberculosis

#5 MeSH descriptor: [Tuberculosis, Extrapulmonary] explode all trees

#6 PTB or EPTB

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 Loop-Mediated Isothermal Amplification

#9 (TB LAMP or LAMP or LOOPAMP):ti,ab,kw

#10 #8 or #9

#11 #7 and #10

Clinicaltrials.gov

Loop-Mediated Isothermal Amplification | Tuberculosis

TB-LAMP | Tuberculosis

WHO ICTRP

tuberculosis and (LAMP or TB-LAMP)

Global Index Medicus

tw:((tw:(tb-lamp)) OR (tw:((loop-mediated isothermal amplification) AND tuberculosis)))

Appendix 2. Data extraction form

TB-LAMP (loop-mediated isothermal amplification) for diagnosing pulmonary tuberculosis in children

Study name:

- Screening number: _____

- Publication month & year: _____

- First author: _____

- Author contact email: _____

- Was the author contacted? Yes / No. If yes, when? _____

- Language of the article: English or Other _____

- Funding: Industry sponsors / Institutional funds / Research grants / not known

-Country of study origin _____

-World Bank Classification: Low / Middle / High (Circle if more than one)

Study details	**Study design**	1. Non-comparative cohort or cross-sectional 2. Comparative cross-sectional–paired design 3. Randomized comparative accuracy 4. Other _____
	Participant selection	1. Consecutive 2. Convenience 3. Random 4. Not reported 5. Others _____
	Status of children at inclusion	1. Clinical symptoms of tuberculosis 2. Chest x-ray suggestive of tuberculosis 3. Contact of patient diagnosed with tuberculosis 4. Positive in latent tuberculosis screening 5. Part of HIV evaluation 6. Part of malnutrition evaluation
	Participants were recruited from	1. Primary care clinics 2. Secondary care hospital 3. Primary care hospital

(Continued)

	4. Community 5. Others ____
Setting of participant recruitment	1. Inpatient 2. Outpatient 3. Both inpatient and outpatient setting 4. Laboratory 5. Not specified 6. Others _____
Children on tuberculosis treatment included (on ATT for more than 7 days)	1. Yes ___ (%) 2. No 3. Not mentioned
Were children with previously treated tuberculosis included	1. Yes ___ (%) 2. No 3. Not mentioned
Inclusion criteria	*(To be described here)*
Index tests	1. TB-LAMP 2. Xpert MTB/RIF Ultra 3. Smear microscopy 4. Other _____ (Circle one or more as appropriate)
Direction of study	1. Prospective 2. Retrospective 3. Ambi-directional 4. Not mentioned
Unit of analysis in this study	Participant / Sample
Number of children recruited	Total: _____, Males: ___ (%), Females: ___ (%)
Number of children included in the analysis	Total: _____, Males: ___ (%), Females: ___ (%)
HIV status	1. Only HIV-positive children included 2. No HIV-positive children were included 3. included both HIV-positive and negative children 4. Not mentioned
Number of children diagnosed with HIV	_____(%)
Nutritional status	1. Only children with malnutrition included 2. No children with malnutrition included 3. Included children with or without malnutrition 4. Not mentioned
Number of children detected to have severe malnutrition	_____(%)

(Continued)

	Criteria used to classify the children to have severe malnutrition	
	Time to initiation of treatment	_____
	Time to diagnosis	_____
	Comments	
TB-LAMP	**Type of specimen** (circle more than 1 if appropriate)	1. Usual expectoration 2. Induced sputum 3. Bronchoalveolar lavage 4. Gastric lavage 5. Nasopharyngeal aspirate 6. Tracheal aspirate / mini-BAL 7. Stool 8. Multiple mixed methods 9. Not mentioned 10. Other ____
	Was the sample processed?	1. No 2. Yes. With NALC-NaOH 3. Yes. With NaOH (Petroff) 4. Unclear - Not mentioned 5. Other _____
	Were TB-LAMP and the reference standard done using the same sample?	1. Yes 2. No 3. Not mentioned
	Where was the test performed	1. Point of care 2. Peripheral lab 3. Intermediate lab 4. Central lab 5. Not mentioned 6. Other _____
	Sample status	1. Fresh 2. Frozen 3. Not mentioned 4. Other _____
	Time taken between sample collection and testing. Is this acceptable?	_____ Yes / No / Unclear
	Version of TB-LAMP	_____
	Comments	
Xpert MTB/RIF Ultra	**Type of specimen**	1. Usual expectoration 2. Induced sputum 3. Bronchoalveolar lavage 4. Gastric lavage

(Continued)

		5. Nasopharyngeal aspirate 6. Tracheal aspirate/mini-BAL 7. Stool 8. Multiple mixed methods 9. Not mentioned Other ____
	Was the sample processed?	1. No 2. Yes. With NALC-NaOH 3. Yes. With NaOH (Petroff) 4. Unclear - Not mentioned 5. Other _____
	Was Xpert MTB/RIF Ultra and culture done using the same sample?	Yes / No
	Sample status	1. Fresh 2. Frozen 3. Not mentioned 4. Other _____
	Where was the test performed	1. Point of care 2. Peripheral lab 3. Intermediate lab 4. Central lab 5. Not mentioned 6. Other _____
	Indeterminate results reported	Yes / No
	Non-determinate results reported	Yes / No
	Time taken between sample collection and testing. Is this acceptable?	_____ Yes / No / Unclear
	Comments	
Smear microscopy	**Type of specimen**	1. Usual expectoration 2. Induced sputum 3. Bronchoalveolar lavage 4. Gastric lavage 5. Nasopharyngeal aspirate 6. Tracheal aspirate / mini-BAL 7. Stool 8. Multiple mixed methods 9. Not mentioned 10. Other ____
	Was the sample processed?	1. No 2. Yes. With NALC-NaOH 3. Yes. With NaOH (Petroff) 4. Unclear - Not mentioned

(Continued)

		5. Other _____
	Were smear microscopy and the reference standard done using the same sample?	1. Yes 2. No 3. Not mentioned
	Sample status	1. Fresh 2. Frozen 3. Not mentioned 4. Other _____
	Where was the test performed	1. Point of care 2. Peripheral lab 3. Intermediate lab 4. Central lab 5. Not mentioned 6. Other _____
	Acid-fast bacilli smear was done using	1. Ziehl-Neelsen 2. Fluorescence microscopy 3. Both of the above 4. Other _____ 5. Not mentioned
	Number of smears done	None / 1 / 2 / 3 / Other _____
	Number of participants who were smear-positive	Number _____ (_____%)
	Number of participants who were smear-negative	Number _____ (_____%)
	Smear type	1. Direct 2. Concentrated 3. Not mentioned
	Sample status	1. Fresh 2. Frozen 3. Not mentioned 4. Other _____
	Where was the test performed	1. Point of care 2. Peripheral lab 3. Intermediate lab 4. Central lab 5. Not mentioned 6. Other _____
	Comments	
Reference standard for tuberculosis detection	**Reference standard used**	1. Culture (solid or liquid) 2. Clinical criteria 3. Composite reference standards including both culture and clinical diagnosis

(Continued)

	If clinical reference standards used	1. Clinical criteria (Graham 2012) 2. Updated clinical criteria (Graham 2015) 3. Clinical scoring system (WHO) 4. Study-specific clinical criteria 5. Decision to treat 6. Not clear
	Solid culture	1. Löwenstein Jensen 2. Middlebrook 7H10 3. Middlebrook 7H11 4. Other _____
	Liquid culture	1. Mycobacteria Growth Indicator Tube - MGIT 960 / 2. BACTEC 460 3. Other _____
	No of specimens collected for performing culture	1. One (Low Quality Reference Standard) 2. More than one (High-Quality Reference Standard)
	Both solid and liquid were used - Circle both above as appropriate	
	Sample status	1. Fresh 2. Frozen 3. Not mentioned 4. Other _____ _____
	Was the sample processed?	1. No 2. Yes. With NALC-NaOH 3. Yes. With NaOH (Petroff) 4. Unclear - Not mentioned 5. Other _____
	Where was the reference standard performed	1. Point of care 2. Peripheral lab 3. Intermediate lab 4. Central lab 5. Not mentioned 6. Other _____
Composite reference standard	Was a composite reference standard used?	1. Yes 2. No
	If yes, described as mentioned in the study	
Contamination status	**Total number of cultures done:**	_____
	Total number of contaminated cultures:	_____

DATA FOR TB-LAMP

All samples	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
All samples	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

**CRS – Composite reference standard*

Smear positive	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Smear negative	**Culture positive**	**Culture negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Smear positive	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

(Continued)

Smear negative	CRS positive	CRS negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

HIV positive	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

HIV negative	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

HIV positive	CRS positive	CRS negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

HIV negative	CRS positive	CRS negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

Severe malnutrition present	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Severe malnutrition absent	**Culture positive**	**Culture negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Severe malnutrition present	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Severe malnutrition absent	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

Data for TB-LAMP in different samples (Example – *this will be expanded based on the different categories of samples found in the included studies)*

Sample: Sputum	Culture positive	Culture negative	Total
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

(Continued)

Sample: Gastric aspirate	**Culture positive**	**Culture negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Sample: Sputum	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Sample: Gastric aspirate	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Sample: _____	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Sample: _____	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			
Sample: _____	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			

(Continued)

Total			
Indeterminate			
Sample: _____	**CRS positive**	**CRS negative**	**Total**
TB-LAMP positive			
TB-LAMP negative			
Total			
Indeterminate			

Data for Xpert MTB/RIF Ultra (only if the study also assessed this with TB-LAMP as a comparative index test)

Xpert MTB/RIF Ultra	**Culture positive**	**Culture negative**	**Total**
Xpert MTB/RIF Ultra positive			
Xpert MTB/RIF Ultra negative			
Total			
Non-determinate			
Xpert MTB/RIF Ultra	**CRS positive**	**CRS negative**	**Total**
Xpert MTB/RIF Ultra positive			
Xpert MTB/RIF Ultra negative			
Total			
Non-determinate			

Data for smear microscopy (only if the study also assessed this with TB-LAMP as a comparative index test)

	Culture positive	**Culture negative**	**Total**
Smear positive			
Smear negative			
Total			
Indeterminate			

(Continued)

	CRS positive	CRS negative	Total
Smear positive			
Smear negative			
Total			
Indeterminate			

Abbreviations: ATT: antitubercular treatment; CRS: composite reference standard; NALC-NaOH: N-acetyl-l-cysteine-sodium hydroxide

Form completed by: Date :

Appendix 3. Methodological quality assessment forms

Assessment of methodological quality of the studies using QUADAS-2 and QUADAS-C

TB-LAMP (loop-mediated isothermal amplification) for diagnosing pulmonary tuberculosis in children

Objectives of our review for reference:

1. To determine the diagnostic accuracy of LC-mNAAT for the detection of pulmonary tuberculosis in children with presumptive pulmonary tuberculosis.
2. To compare the diagnostic accuracy of LC-mNAAT and Xpert MTB/RIF Ultra for the detection of pulmonary tuberculosis in children with presumptive pulmonary tuberculosis.
3. To compare the diagnostic accuracy of TB-LAMP and smear microscopy for detecting pulmonary tuberculosis in children when TB-LAMP is considered a replacement test for smear microscopy.
4. To determine the diagnostic accuracy of TB-LAMP for the detection of pulmonary tuberculosis if used as an add-on test among sputum smear-negative children.
5. To investigate potential sources of heterogeneity in the diagnostic accuracy of TB-LAMP due to factors such as HIV status, smear status, tuberculosis burden, and setting.

Our protocol summary for reference:

Participants	Children aged 0 to 9 years who are presumed to have pulmonary tuberculosis with or without HIV infection
Target condition	Pulmonary tuberculosis
Index test A	TB-LAMP
Index test B	Xpert MTB/RIF Ultra
Index test C	Smear microscopy
Reference standard	1. **Culture:** either a solid culture or automated liquid culture 2. **Composite reference standard:** either a positive culture or a clinical diagnosis based on clinical criteria/clinical scoring system.

Study name:

Screening number:

Publication month & year:

Study design

Which of the following study designs does the primary study most strongly resemble?	1. Cross-sectional (non-comparative) 2. Comparative accuracy (a) Fully paired (b) Randomized

Flow diagram

Domain 1: Participant selection

LC-mNAAT for diagnosing pulmonary tuberculosis in children

Relevant details:

Single test accuracy (QUADAS-2)		**Answers for TB-LAMP**	**Answers for Xpert MTB/RIF Ultra**	**Answers for smear microscopy**
Signalling questions	1.1 Was a consecutive or random sample of participants enroled?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	1.2 Was a case-control design avoided?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	1.3 Did the study avoid inappropriate exclusions?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	1.4 Could the selection of participants have introduced bias?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear
Concerns regarding applicability	1.5 Were there concerns that the included participants do not match the review question?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear

Comparative accuracy (QUADAS-C)		**TB-LAMP versus Xpert MTB/RIF Ultra**	**TB-LAMP versus smear microscopy**
Signalling questions	C1.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes / No	Yes / No
	C1.2 Was a fully paired or fully randomized design or a partially paired randomized design used?	Yes / Unclear	Yes / Unclear
	C1.3 Was the allocation sequence random?[a]	Yes / No / Unclear / NA	Yes / No / Unclear / NA

(Continued)

	C1.4 Was the allocation sequence concealed until participants were enroled and assigned to index tests?[a]	Yes / No / Unclear / NA	Yes / No / Unclear / NA
Risk of bias	Could the selection of participants have introduced bias in the comparison?	Low / High / Unclear	Low / High / Unclear

Footnotes:

[a]Only applicable to randomized designs.

NA: not applicable.

Signalling question (1.1): was a consecutive or random sample of participants enroled?

We answered 'yes' if the participant enrolment was either consecutive or random and 'no' if the selection was based on convenience; 'unclear' if not described in the study.

Signalling question (1.2): was a case-control design avoided?

We answered 'yes' for all studies by default since we decided to avoid multiple group designs in our review.

Signalling question (1.3): did the study avoid inappropriate exclusions?

We expected studies to include a representative population with presumptive TB that may include people who are treatment-naïve and who have previously received treatment for TB, irrespective of sputum smear status or the result of other related investigations. We answered 'yes' if the study included a representative sample of patients, including both smear-positive and smear-negative individuals. We answered 'no' if the study included primarily or exclusively smear-positive or smear-negative patients or if the study included primarily or exclusively patients who had undergone previous treatment (retreatment patients). We amswered 'unclear' if we were unable to make a judgement of yes or no based on the available information.

Risk of bias (1.4): could the selection of participants have introduced bias?

If only one signalling question was answered 'no' or 'unclear', we discussed further before making the risk of bias judgement for the domain. We judged 'low if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judge 'unclear' if all or most signalling questions were answered unclear.

Applicability (1.5): Were there concerns that the included participants and setting do not match the review question?

We were interested in how the index test was performed in adults and adolescents who were evaluated for Pulmonary Tuberculosis as they would be in routine practice.

Low: if patients were evaluated in local hospitals, community or primary care centres or if the sample was collected at a peripheral centre but processed in a tertiary laboratory.

High: if patients were evaluated exclusively as inpatients in tertiary care centres or medical colleges, or if the specimens were from stored samples in a central laboratory, or if the setting did not match the review question, for example using the index for decisions about the need for airborne isolation.

Unclear: if the clinical setting was not reported or the information available was insufficient to make a judgement. We also answered 'unclear' if the index test was done at a central-level laboratory, and the clinical setting was not reported for the following reason: it is difficult to tell if a given reference laboratory provided services mainly to very sick patients (inpatients in tertiary care) or to all patients, including very sick patients and those with less severe disease (primary, secondary, and tertiary care).

Signalling question (C1.1): was the risk of bias for each index test judged 'low' for this domain?

This question should be answered 'no' if one or more index tests in the comparison were classified as 'high risk' or 'unclear risk' in a QUADAS-2 domain; 'yes' if all were judged 'low risk'.

Signalling question (C1.2): was a fully paired or randomized design used?

Since we have decided to include only paired and fully randomized study designs in our protocol, this question was always answered answered 'Yes'.

Signalling question (C1.3): was the allocation sequence random?[†]

If computer-generated random numbers, random number tables, or drawing lots were utilized for randomization, then we answered 'yes'. We answered 'no' to non-random allocation sequences such as alternation, procedures based on dates, or investigators' subjective judgements; We answered'unclear' if the allocation process was not described in detail.

Signalling question (C1.4): was the allocation sequence concealed until participants were enroled and assigned to index tests?[†]

We answered 'yes' for central randomization methods or sealed envelopes; 'no' if the allocation sequence was not hidden; if the explanation was inadequate, it should be labelled as 'unclear'. We answered 'NA' if a paired design was used.

Risk of bias (C1.5): could the selection of participants have introduced bias in the comparison?

If 'yes' to questions C1.1 to C1.4, the risk of bias was deemed to be 'low' (questions C1.3 and C1.4 only apply to randomized designs). We considered a 'high risk of bias' judgement if at least one question was answered 'no', and if the bias connected with the design element was sufficiently troublesome that the domain as a whole was deemed problematic. If 'unclear' was marked for any of C1.1 to C1.4 then the entire domain was marked 'unclear'.

Domain 2: Index Test

LC-mNAAT for diagnosing pulmonary tuberculosis in children

Relevant details:

Single test accuracy (QUADAS-2)		**Answers for TB-LAMP**	**Answers for Xpert MTB/RIF Ultra**	**Answers for smear microscopy**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	2.2 If a threshold was used, was it prespecified?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear
Concerns regarding applicability	2.4 Were there concerns that the index test, its conduct, or its interpretation differs from the review question?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear

Comparative accuracy (QUADAS-C)		**TB-LAMP versus Xpert MTB/RIF Ultra**	**TB-LAMP versus smear Microscopy**
Signalling questions	C2.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes / No	Yes / No
	C2.2 Were the index test results interpreted without knowledge of the results of the other index test?	Yes / No / Unclear / NA	Yes / No / Unclear / NA
	C2.3 Is undergoing one index test unlikely to affect the performance of the other index test?	Yes / No / Unclear / NA	Yes / No / Unclear / NA

(Continued)

	C2.4 Were the index tests conducted and interpreted without advantaging one of the tests?	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Low / High / Unclear	Low / High / Unclear

Footnotes:

NA: not applicable.

Signalling question (2.1): were the index test results interpreted without knowledge of the results of the reference standard?

We answered 'yes' if the index test in question was done and interpreted by different people without the knowledge of the results of other index tests and the reference standard or if the index test and reference standards were done in different laboratories. Since clinical diagnosis was part of the reference standard, if the index test interpretation and the clinical diagnosis are done by the same person, there will be bias. We answered'no' if the index test interpreter was aware of the clinical history of the participant or the results of the reference standard or other index tests. We answered 'unclear' if this concept was not clearly explained in the study.

Signalling question (2.2): if a threshold was used, was it prespecified?

We answered 'yes' for all studies since the threshold is predefined for TB-LAMP and Xpert. For smear microscopy, we expected the study to consider the result positive if at least one acid-fast bacillus (AFB) was identified in any smear, and this should be explained. We answered 'yes' if the smear microscopy AFB count threshold for a positive test (1+, 2+, etc.) was explained in the methods, 'no' if a different threshold was used, and 'unclear' if there was a description of the same.

Risk of bias (2.3): could the conduct or interpretation of the index test have introduced bias?

If only one signalling question was answered 'no' or 'unclear', we discussed it further before making the risk of bias judgement for the domain. We judged 'low if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judge 'unclear' if all or most signalling questions were answered unclear.

Applicability (2.4): Were there concerns that the index test, its conduct, or its interpretation is different from the review question?

We judged 'low' if the index test was performed as recommended by the manufacturer. If a particular study evaluated different types of specimens such as sputum, gastric aspirate, tracheal aspirate etc, we used the following rule: if ≥ 75% of the specimen types were processed per the manufacturer's instructions, then we judged as 'low concern'.

We answered 'high' if the persons administering and interpreting the test clearly did not follow the manufacturer's instructions. In the case of multiple types of specimens, if < 50% of the specimen types were processed according to the book or as per the manufacturer's instructions, we judged it as 'high concern'.

We answered 'unclear' if the description of the test processes was insufficient to make a yes or no judgement. If a study evaluated several different types of specimens, if at least 50% to 74% of the specimen types were processed according to the manufacturer's instructions, or if we could not tell, we judged it as an 'unclear concern'.

Signalling question (C2.1): was the risk of bias for each index test judged 'low' for this domain?

We answered 'yes' if the answer to signalling questions 2.1 and 2.2 was 'yes'. We answered 'no' if one of 2.1 or 2.2 was a 'no' or 'unclear'.

Signalling question C2.2: were the index test results interpreted without knowledge of the results of the other index test(s)?

Blinding is necessary as smear microscopy and TB-LAMP involve subjective interpretation. We answered 'yes' if the index tests and the reference standard were performed in different laboratories by different people without the knowledge of other tests. We answered 'no' if the person who interpreted smear microscopy and TB-LAMP had access to the results of the culture or the clinical history of the patient. We answered 'unclear' if there was insufficient description to enable a judgement of no or yes.

Signalling question (C2.3): is undergoing one index test unlikely to affect the performance of the other index test(s)?

Since all index tests are performed on samples that are likely to be collected in the same way and produce findings that are objectively calculated (except TB-LAMP), the answer was always 'yes', as one index test cannot affect or interfere with the outcome of an index test that is conducted later or simultaneously. However, studies using mixed methods of sample collection of sputum samples after bronchoscopy would have a higher yield than pre-bronchoscopy sputum (Ali 2022). So, if multiple sputum collection methods were performed within

the same study, the bronchoalveolar test could positively affect the performance of sputum production post-bronchoscopy. Stool sample collection and gastric lavage are immune to performance changes if the index test was performed on different samples at different orders. We answered 'no' only if different sputum collection methods were used to compare the two index tests, especially if one sputum was collected after bronchoscopy. We answered 'unclear' if mixed methods of sputum collection were used in the study, but it was not clearly explained in the study methods section how it was handled across the index tests.

Signalling question (C2.4): were the index tests conducted and interpreted without advantaging one of the tests?

If the index tests that are being compared were performed on the same sample or sample, which was processed in the same way, or if the unprocessed sample was used for both index tests uniformly across the study, we answered 'yes'. If there was a difference in the method of sample collection, which is known to increase the yield of a positive result, that was used for the two index tests, such as sputum induction for one index test and normal expectoration for the other, we answered 'no'; 'unclear' if no information available to make the judgement.

Could the conduct or interpretation of the index tests have introduced bias in the comparison?

If the responses to C2.1 to C2.4 were all answered 'yes', the risk of bias was deemed to be 'low'. We considered a 'high risk of bias' judgement if any of C2.1 to C2.4 was answered 'no'. If 'unclear' was recorded for any of C2.1 to C2.4, then the entire domain was judged 'unclear'.

Domain 3: Reference standard

LC-mNAAT for diagnosing pulmonary tuberculosis in children

a – culture reference standard

b – composite reference standard

Relevant details:

Single test accuracy (QUADAS-2)		**Answers for TB-LAMP**	**Answers for Xpert MTB/RIF Ultra**	**Answers for smear microscopy**
Signalling questions	3.1a Is the culture reference standard likely to correctly classify the target condition (pulmonary tuberculosis)?	Yes / Unclear	Yes / Unclear	Yes / Unclear
	3.1b Is the composite reference standard likely to correctly classify the target condition (pulmonary tuberculosis)?	Unclear	Unclear	Unclear
	3.2a Were the reference standard results interpreted without knowledge of the results of the index test?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	3.2b Were the reference standard results interpreted without knowledge of the results of the index test?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	3.3a Could the reference standard, its conduct, or its interpretation have introduced bias?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear
	3.3b Could the reference standard, its conduct, or its interpretation have introduced bias?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear
Concerns regarding applicability	3.4a Were there concerns that the target condition as defined by the reference standard does not match the review question?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear

(Continued)

	3.4b Were there concerns that the target condition as defined by the reference standard does not match the review question?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear

Comparative accuracy (QUADAS-C)		**TB-LAMP versus Xpert MTB/RIF Ultra**	**TB-LAMP versus smear Microscopy**
Signalling questions	C3.1a Was the risk of bias for each index test judged 'low' for this domain?	Yes / No / Unclear	Yes / No / Unclear
	C3.1b Was the risk of bias for each index test judged 'low' for this domain?	Yes / No / Unclear	Yes / No / Unclear
	C3.2a Did the reference standard avoid incorporating any of the index tests?	Yes	Yes
	C3.2b Did the reference standard avoid incorporating any of the index tests?	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	C3.3a Could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?	Low / High / Unclear	Low / High / Unclear
	C3.3b Could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?	Low / High / Unclear	Low / High / Unclear

'a' refers to culture as a reference standard and 'b' refers to a composite reference standard.

Signalling question (3.1a): is the culture reference standard likely to correctly classify the target condition (pulmonary tuberculosis)?

We answered 'yes' if a study used any of the solid or automated liquid culture methods, or a combination of these methods. We answered 'no' if the study did not use culture methods or a clinical composite reference standard. We answered 'unclear' if we were unable to make a judgement of 'yes' or 'no'.

Signalling question (3.1b): is the composite reference standard likely to correctly classify the target condition (pulmonary tuberculosis)?

The purpose of a composite reference standard is to diagnose children in whom tuberculosis was not detected by culture. The composite reference standard could be defined differently in each study. We identified children as having tuberculosis regardless of the criteria used in the articles; study-specific criteria for defining tuberculosis were accepted. The key mandate is the initiation of tuberculosis treatment following a diagnosis of tuberculosis. We answered 'unclear' for all studies due to the nature of the reference standard were not specific (Kay 2022).

Signalling question (3.2a): was the culture reference standard results interpreted without knowledge of the results of the index test?

We answered 'yes' if the reference standard was automated, such as MGIT culture or if the culture process happened in a different laboratory where the TB-LAMP smear microscopy or Xpert tests were performed. We answered 'no' if the reference standard result, including the clinical diagnosis, was interpreted knowing the result of the index test(s). We answered 'unclear' if such details were not described in the study.

Signalling question (3.2b): were the composite standard results interpreted without knowledge of the results of the index test?

We answered 'yes' if the interpreter or clinician who made the diagnosis based on the composite reference standard was blinded to the result of the index test(s). We answered 'no' if the clinical diagnosis was made knowing the result of the index test(s). We answered 'unclear' if such details were not described in the study.

Risk of bias (3.3 a): could the reference standard, its conduct, or its interpretation have introduced bias?

If only one signalling question (3.1 a and 3.2 a) was answered 'no' or 'unclear', we discussed it further before making the risk of bias judgement for the domain. We judged 'low' if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judged 'unclear' if all or most signalling questions were answered unclear.

Risk of bias (3.3 b): could the reference standard, its conduct, or its interpretation have introduced bias?

If only one signalling question (3.2 a and 3.2 b) was answered 'no' or 'unclear', we discussed it further before making the risk of bias judgement for the domain. We judged 'low' if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judged 'unclear' if all or most signalling questions were answered unclear.

Applicability (3.4a): Were there concerns that the target condition, as defined by the reference standard, does not match the question?

We judged 'high concern' if the culture methods used in the study did not mention if *Mycobacterium tuberculosis* (or a specific contaminant) grew in the culture. We judged 'low concern' if speciation was performed appropriately and 'unclear concern' if speciation was not mentioned.

Applicability (3.4b): Were there concerns that the target condition, as defined by the reference standard, does not match the question?

We judged 'low' if treatment was initiated after diagnosing using the composite reference standard. We judged 'high' if treatment was not initiated after using the composite reference standard. We judged 'unclear' if we could not judge low or high concern based on the available information.

Signalling question (C3.1a): was the risk of bias for each index test judged 'low' for this domain?

This question was answered 'no' even if one of the signalling questions 3.1a and 3.2a is classified as 'high' or 'unclear' for this QUADAS-2 domain for culture reference standard; 'yes' if both were judged 'low' risk.

Signalling question (C3.1a): was the risk of bias for each index test judged 'low' for this domain?

This question was answered 'no' even if one of the signalling questions 3.1b and 3.2b is classified as 'high' or 'unclear' for this QUADAS-2 domain for composite reference standard; 'yes' if both were judged 'low' risk.

Signalling question (C3.2a): did the reference standard avoid incorporating any of the index tests?

We answered 'yes' if the culture was used as the index tests were part of this reference standard.

Signalling question (C3.2b): did the reference standard avoid incorporating any of the index tests?

We answered 'yes' if it was explicitly stated that TB-LAMP, smear microscopy, and Xpert MTB/RIF Ultra were not part of the reference standard; 'no' if they were part of the reference standard. We answered 'unclear' only if the reference standard was not described adequately with respect to the inclusion/exclusion of the index tests. We also answered 'unclear 'if the authors used a composite or clinical reference standard in which the comparator index test in question (smear microscopy or Xpert MTB/RIF Ultra) was one of the components of the reference standard. In this case, the study may lead to incorporation bias in which there is no blinding of the reference standard to the index test. Incorporation bias may increase the agreement between the index test results and reference standard, thereby overestimating diagnostic accuracy.

Risk of bias (C3.3a): could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?

If 'yes' to signalling questions C3.1a and C3.2a, the risk of bias was deemed to be 'low' for reference standards a and b, respectively. We considered a 'high risk of bias' judgement if at least one question was answered 'no', and if the bias associated with the design element raises enough red flags to make the domain as a whole problematic. We answered 'unclear' if the administration of the composite reference standard that includes clinical diagnosis was not sufficiently described in terms of its conduct and interpretation.

Risk of bias (C3.3b): could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?

If 'yes' to signalling questions C3.1b and C3.2b, risk of bias was deemed to be 'low' for reference standards a and b respectively. We considered a 'high risk of bias' judgement if at least one question was answered 'no', and if the bias associated with the design element raises enough red flags to make the domain as a whole problematic. We answered 'unclear' if the administration of the composite reference standard that includes clinical diagnosis is not sufficiently described in terms of its conduct and interpretation.

Domain 4: Flow and timing

LC-mNAAT for diagnosing pulmonary tuberculosis in children

(Continued)

Relevant details:

Single test accuracy (QUADAS-2)		**Answers for TB-LAMP**	**Answers for Xpert MTB/RIF Ultra**	**Answers for smear microscopy**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standards?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	4.2 Did all participants receive a reference standard?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	4.3 Did all participants receive the same reference standard?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
	4.4 Were all participants included in the analysis?	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	Could the participant flow have introduced bias?	Low / High / Unclear	Low / High / Unclear	Low / High / Unclear

Comparative accuracy (QUADAS-C)		**TB-LAMP versus Xpert MTB/RIF Ultra**	**TB-LAMP versus smear microscopy**
Signalling questions	C4.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes / No	Yes / No
	C4.2 Was there an appropriate interval between the index tests?	Yes / No / Unclear	Yes / No / Unclear
	C4.3 Was the same reference standard used for all index tests?	Yes / No / Unclear	Yes / No / Unclear
	C4.4 Were the proportions and reasons for missing data similar across index tests?	Yes / No / Unclear	Yes / No / Unclear
Risk of bias	Could the participant flow have introduced bias in the comparison?	Low / High / Unclear	Low / High / Unclear

Signalling question (4.1): was there an appropriate interval between the index test and reference standard?

We expected to find for most included studies that specimen index tests and culture were obtained simultaneously when participants were evaluated for presumed tuberculosis. Even if there were a delay of several days between index tests and reference standards, tuberculosis is a chronic disease, and we consider misclassification of disease status to be unlikely as long as treatment was not initiated in the interim. We answered 'yes' if the index test and the reference standard were performed at the same time or if the time interval was seven days or less; 'no' if the time interval was greater than seven days; and 'unclear' if these details were not available (Kay 2022).

Signalling question (4.2): did all participants receive the same reference standard?

We answered 'yes' if all participants in the study or a subset of participants in the study (for whom we extracted data) received the acceptable reference standard, either culture or a composite reference standard. Regarding culture, we acknowledge that it is possible that some specimens could undergo solid culture and others liquid culture as the reference standard. We answered 'no' if not all participants received the same reference standard. We answered 'unclear' If we could not judge 'yes' or 'no'.

Signalling question (4.3): were all participants included in the analysis?

We determined the answer to this question by comparing the number of participants enrolled with the number of participants included in the 2×2 tables. We observed if the study authors reported the number of inconclusive test results. We answered 'yes' if the number

of participants enrolled was clearly stated and corresponded to the number presented in the analysis or if exclusions were adequately described; 'no' if participants were missing or excluded from the analysis and there was no explanation given; 'unclear' if insufficient information was given to assess whether participants were excluded from the analysis.

Risk of bias (4.5): could the participant flow have introduced bias?

If only one signalling question was answered 'no' or 'unclear', we discussed it further before making the risk of bias judgement for the domain. We judged 'low' if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judged 'unclear' if all or most signalling questions were answered unclearly.

C4.1 Was the risk of bias for each index test judged 'low' for this domain?

This question was answered 'no' if one of the signalling questions 4.1 to 4.3 is classified as 'high' or 'unclear' in this QUADAS-2 domain and 'yes' if all were judged 'low'.

C4.2 Was there an appropriate interval between the index tests?

We answered 'yes' if all the tests (TB-LAMP, Xpert MTB/RIF Ultra, smear microscopy) were performed at the same time or if the time interval was seven days or less; 'no' if the time interval was greater than seven days; and 'unclear' if these details were not available.

C4.3 Was the same reference standard used for all index tests?

We answered 'yes' if either a solid or liquid culture or clinical criteria were used for all index tests either alone or in combination; 'no' if the same reference standard was not used for the two index tests being compared; 'unclear' if not described adequately in the study.

C4.4 Were the proportions and reasons for missing data similar across index tests?

If the proportion of missing data across both index tests is more than 5%, we answered' no'; if not, we answered 'yes'. If the reasons for missing data were not explained clearly or provided, we answered 'unclear'.

Could the participant flow have introduced bias in the comparison?

If 'yes' responses were given to signalling questions C4.1 to C4.4, the risk of bias was deemed 'low.' We considered a 'high risk of bias' judgement if at least one question was answered 'no,' especially if the design raises enough red flags to make the domain as a whole problematic; 'unclear risk of bias' if one of the responses was judged unclear and all other responses were 'yes'.

Abbreviations: CRS: composite reference standard; MGIT: Mycobacterium Growth Indicator Tube; TB-LAMP: tuberculosis loop-mediated isothermal amplification; WHO: World Health Organization.

Appendix 4. Additional forest plots

Additional forest plots showing results by HIV status (Figure 5), by age group for respiratory specimens (Figure 6), and for stool (Figure 7), and comparisons of index tests (Figure 8).

Figure 5. Forest plot of the accuracy of TB-LAMP in children living with HIV using different specimens. Abbreviations: CLHIV: children living with HIV; FN: false negative; FP: false positive; NPA: nasopharyngeal aspirate; PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TN: true negative; TP: true positive

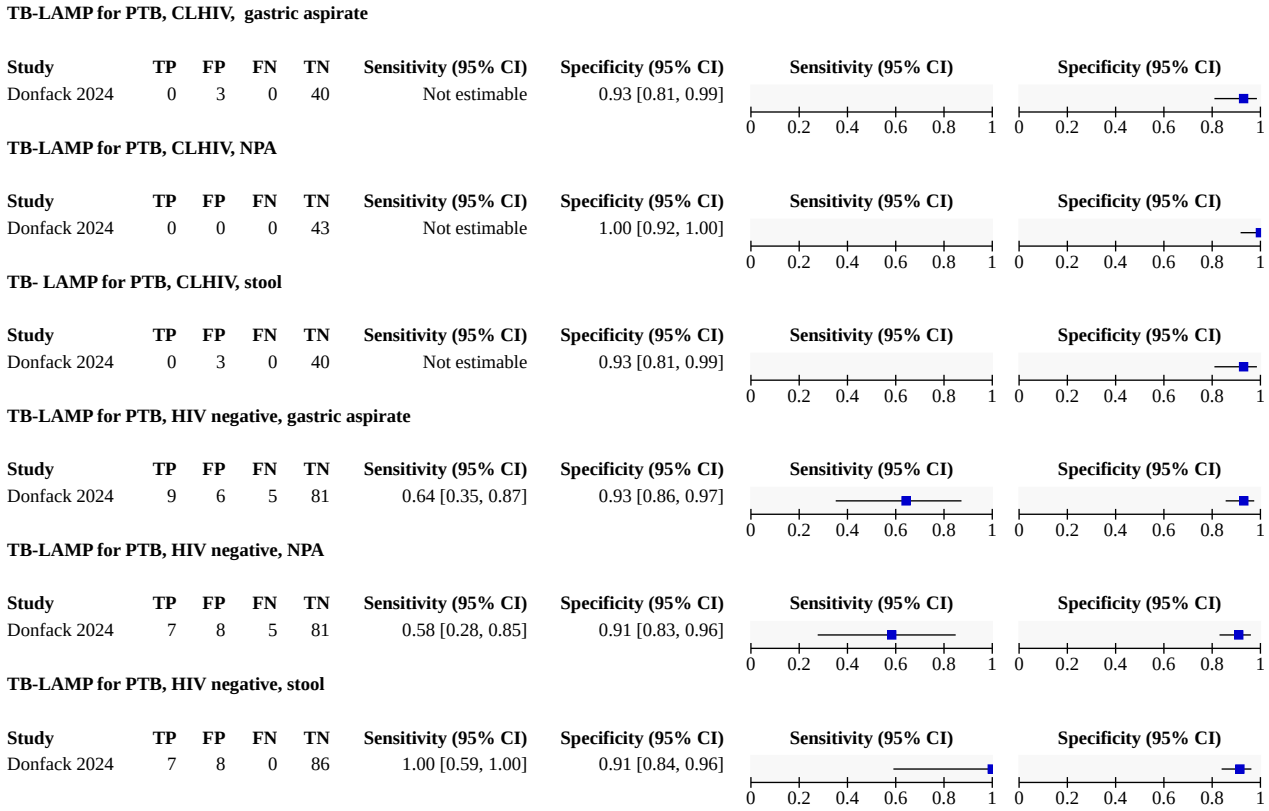
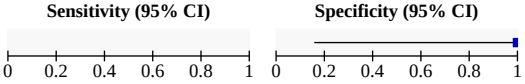


Figure 6. Forest plot of the accuracy of TB-LAMP in children using all specimens except stool, by age group.

Abbreviations: BAL: bronchoalveolar lavage; FN: false negative; FP: false positive; NPA: nasopharyngeal aspirate; PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TN: true negative; TP: true positive

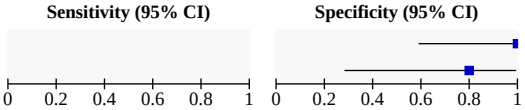
TB-LAMP for PTB, < 1 year, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	2	Not estimable	1.00 [0.16, 1.00]



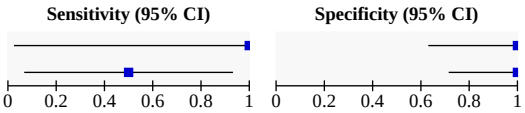
TB-LAMP for PTB, 1 to 4 years, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Yadav 2021	0	1	0	4	Not estimable	0.80 [0.28, 0.99]



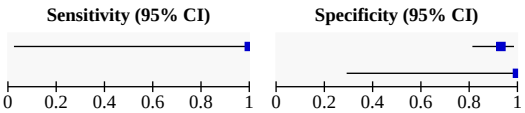
TB-LAMP for PTB, 5 to 9 years, sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	8	1.00 [0.03, 1.00]	1.00 [0.63, 1.00]
Yadav 2021	2	0	2	11	0.50 [0.07, 0.93]	1.00 [0.72, 1.00]



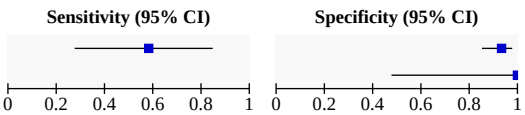
TB-LAMP for PTB, 5 to 9 years, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	3	0	41	1.00 [0.03, 1.00]	0.93 [0.81, 0.99]
Yadav 2021	0	0	0	3	Not estimable	1.00 [0.29, 1.00]



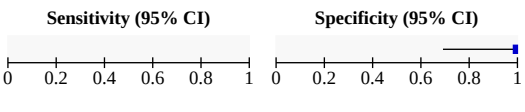
TB-LAMP for PTB, 1 to 4 years, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	7	5	5	71	0.58 [0.28, 0.85]	0.93 [0.85, 0.98]
Yadav 2021	0	0	0	5	Not estimable	1.00 [0.48, 1.00]



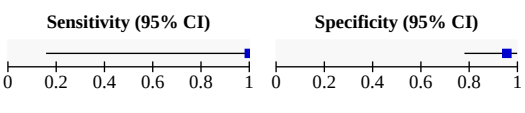
TB-LAMP for PTB, <1 year, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]



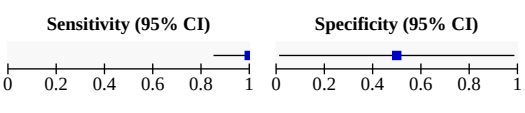
TB-LAMP for PTB, 1 to 4 years, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	2	1	0	22	1.00 [0.16, 1.00]	0.96 [0.78, 1.00]



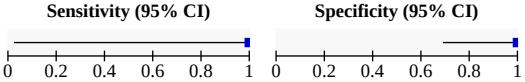
TB-LAMP for PTB, 5 to 9 years, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	23	1	0	1	1.00 [0.85, 1.00]	0.50 [0.01, 0.99]



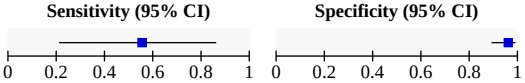
TB-LAMP for PTB, <1 year, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	0	0	10	1.00 [0.03, 1.00]	1.00 [0.69, 1.00]



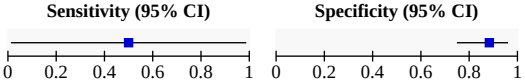
TB-LAMP for PTB, 1 to 4 years, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	5	3	4	76	0.56 [0.21, 0.86]	0.96 [0.89, 0.99]



TB-LAMP for PTB, 5 to 9 years, NPA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	1	5	1	38	0.50 [0.01, 0.99]	0.88 [0.75, 0.96]



TB-LAMP for PTB, <1 year, BAL

Figure 6. (Continued)

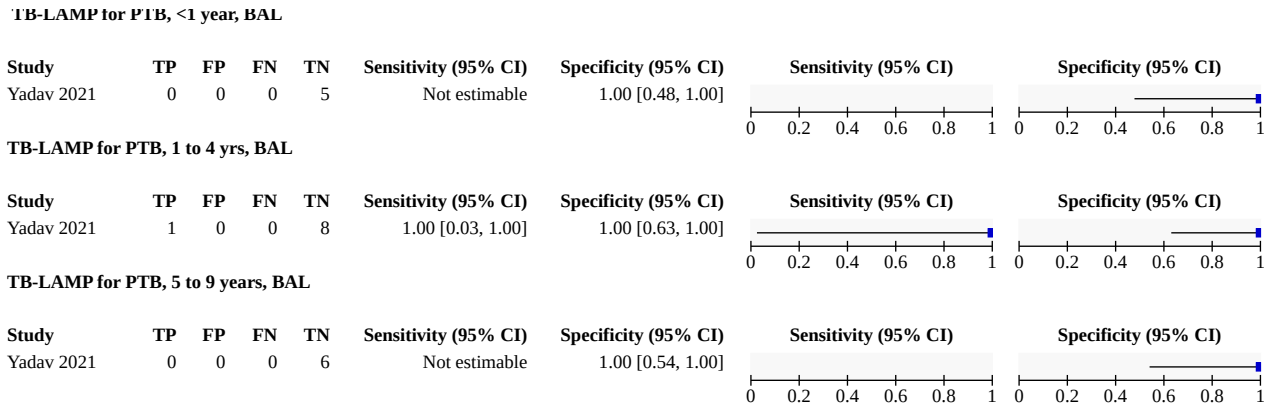


Figure 7. Forest plot of the accuracy of TB-LAMP in children using stool specimen, by age group. Abbreviations: PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TN: true negative; TP: true positive

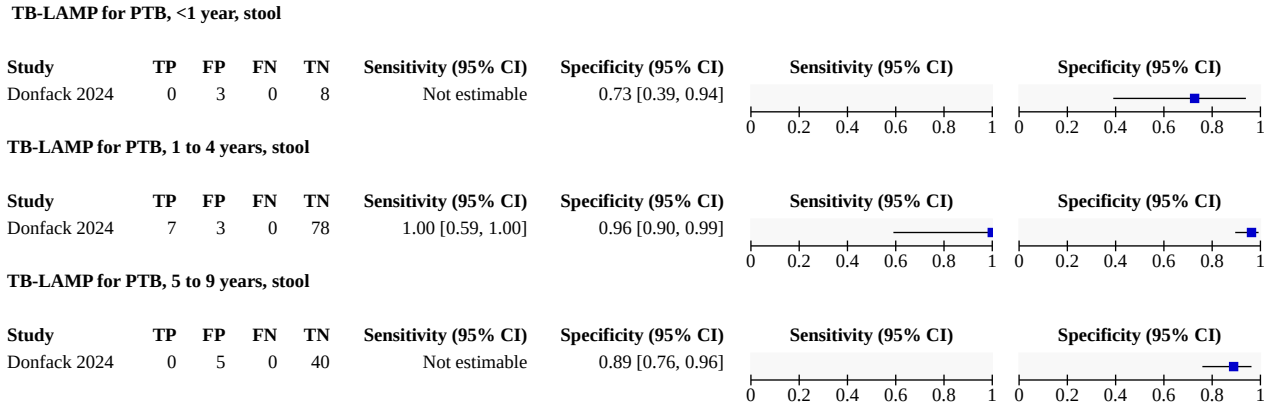


Figure 8. Comparison of TB-LAMP, Xpert MTB/RIF Ultra, and smear microscopy.
Abbreviations: PTB: pulmonary tuberculosis; TB-LAMP: tuberculosis loop-mediated isothermal amplification; TN: true negative; TP: true positive

TB-LAMP for PTB, respiratory specimens (sputum, BAL & tracheal aspirate)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]
Promsena 2022	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]
Yadav 2021	3	2	2	38	0.60 [0.15, 0.95]	0.95 [0.83, 0.99]

Xpert Ultra, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	1	0	1	1	0.50 [0.01, 0.99]	1.00 [0.03, 1.00]

Smear microscopy, respiratory specimens

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bojang 2016	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]
Promsena 2022	2	0	0	4	1.00 [0.16, 1.00]	1.00 [0.40, 1.00]
Yadav 2021	0	1	5	39	0.00 [0.00, 0.52]	0.97 [0.87, 1.00]

TB-LAMP for PTB, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donfack 2024	9	9	5	121	0.64 [0.35, 0.87]	0.93 [0.87, 0.97]
Promsena 2022	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]

Xpert Ultra, gastric aspirate

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	0	1	0	21	Not estimable	0.95 [0.77, 1.00]

Smear microscopy, gastric aspirate

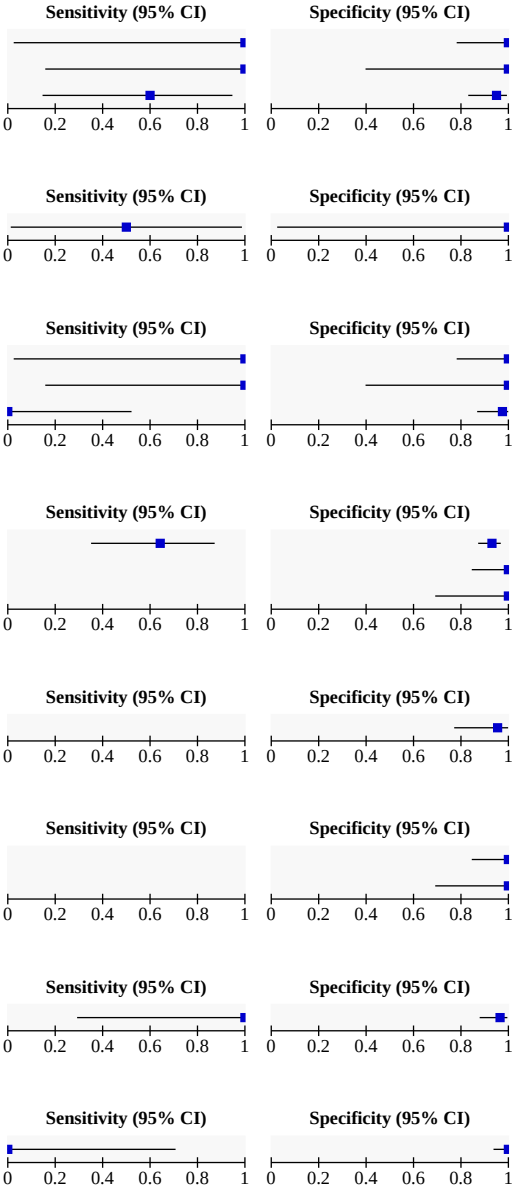
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Promsena 2022	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Yadav 2021	0	0	0	10	Not estimable	1.00 [0.69, 1.00]

TB-LAMP for PTB, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	3	2	0	55	1.00 [0.29, 1.00]	0.96 [0.88, 1.00]

Smear microscopy, gastric lavage

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Yadav 2021	0	0	3	57	0.00 [0.00, 0.71]	1.00 [0.94, 1.00]



HISTORY

Protocol first published: Issue 9, 2023

CONTRIBUTIONS OF AUTHORS

LRI conceived the idea, trained the team, supervised the work, co-ordinated the tasks, contributed to the writing of the review, and edited and reviewed the final manuscript.

MKS, TE, VA, and AB were involved in screening the articles. JD aided in resolving disagreements if there were any discrepancies between the review authors.

MKS, VA, JD, AB, TE, and BD were involved in extracting data, assessing the risk of bias and applicability, and writing a few sections of the manuscript. LR acted as an arbitrator during data extraction and methodological quality assessment.

JD trained the team, developed the data extraction form, led modifications of the QUADAS-2 and QUADAS-C tools to the review question, and wrote sections of the manuscript.

WR and PR gave technical input. KS assisted YT in data analysis and reviewed the manuscript.

AK and NI reviewed the protocol, interpreted the results, and gave input on the final review.

YT provided methodological and statistical supervision, performed statistical analysis, critically reviewed the manuscript, and mentored the team.

All review authors reviewed and approved the final version of the review.

DECLARATIONS OF INTEREST

LRI, MKSN, BD, VA, AB, and PR are employed at ICMR and have no known conflicts of interest.

JD, WR, TEC, and KS have no known conflicts of interest.

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

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

YT is a co-convenor of the Cochrane Screening and Diagnostic Tests Methods Group and an editor of the Cochrane Infectious Diseases Group. YT was not involved in the editorial processing of this review.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine (LSTM), UK

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External sources

- Foreign, Commonwealth, and Development Office (FCDO), UK

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- World Health Organization (WHO), Switzerland

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Title

We changed the title from "TB-LAMP (loop-mediated isothermal amplification) for diagnosing pulmonary tuberculosis in children" to "Low-complexity manual nucleic acid amplification tests for pulmonary tuberculosis in children." This review informed part of the 2024 update of the WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection. The Guideline Development Group meeting was held from 6-10 May 2024 in Geneva, Switzerland. The WHO introduced a class-based recommendation approach in December 2020 instead of an approach based on individual technologies. Therefore, we changed the title to align with the WHO policy.

Objectives

We made minor changes to the objectives to be consistent with the title.

Index test

As this review informed a WHO guideline update, we excluded in-house assays and included only design-locked, marketed test technologies as suggested by the WHO.

Searching for other resources

We added additional information regarding the WHO public call by inserting this statement: "A WHO public call was made between December 2023 and 15 February 2024 for ongoing and unpublished studies from manufacturers and researchers."

Methodological quality assessment

We made the following modifications to QUADAS-2 and QUADAS-C to be consistent with the other five systematic reviews in our generic protocol for the 2024 WHO policy update. The generic protocol is available at https://osf.io/26wg7/.

For the judgement regarding the risk of bias for all the domains, if only one signalling question was answered 'no' or 'unclear', we discussed further before making the risk of bias judgement for the domain. We judged 'low' if all signalling questions were answered 'yes'. We judged 'high' if all or most signalling questions were answered 'no'. We judged 'unclear' if all or most signalling questions were answered 'unclear'.

Signalling question (1.3): did the study avoid inappropriate exclusions?:

We expected studies to include a representative population with presumptive tuberculosis that may include people who are treatment-naïve and who have previously received treatment for tuberculosis, irrespective of sputum smear status or the result of other related investigations. We answered 'yes' if the study included a representative sample of patients, including both smear-positive and smear-negative individuals. We answered 'no' if the study included primarily or exclusively smear-positive or smear-negative patients or if the study included primarily or exclusively patients who had undergone previous treatment (retreatment patients). We answered 'unclear' if we could not judge yes or no based on the available information.

Applicability (1.5): are there concerns that the included participants and setting do not match the review question?

We were interested in how the index test was performed in adults and adolescents who were evaluated for pulmonary tuberculosis as they would be in routine practice.

Low: if patients were evaluated in local hospitals, community or primary care centres or if the sample was collected at a peripheral centre but processed in a tertiary laboratory.

High: if patients were evaluated exclusively as inpatients in tertiary care centres or medical colleges, or if the specimens were from stored samples in a central laboratory, or if the setting did not match the review question, for example, using the index for decisions about the need for airborne isolation.

Unclear: if the clinical setting was not reported or the information available is insufficient to make a judgement. We also answered 'unclear' if the index test was done at a central-level laboratory or if the clinical setting was not reported for the following reason: it is difficult to tell if a given reference laboratory provided services mainly to very sick patients (inpatients in tertiary care) or to all patients, including very sick patients and those with less severe disease (primary, secondary, and tertiary care).

Applicability (2.4): are there concerns that the index test, its conduct, or its interpretation is different from the review question?

We judged 'low' if the index test was performed as recommended by the manufacturer. If a particular study evaluated different types of specimens, such as sputum, gastric aspirate, tracheal aspirate, etc., we used the following rule: if ≥ 75% of the specimen types were processed per the manufacturer's instructions, then we judge them as 'low concern'.

We answered 'high' if the persons administering and interpreting the test clearly did not follow the manufacturer's instructions. In the case of multiple types of specimens, if < 50% of the specimen types were processed according to the book or as per the manufacturer's instructions, we judged it as 'high concern'.

We answered 'unclear' if the description of the test processes is insufficient to make a yes or no judgement. If a study evaluated several different types of specimens, if at least 50% to 74% of the specimen types were processed according to the manufacturer's instructions, or if we could not tell, we judged it as an 'unclear concern'.

Signalling question (3.1a): is the culture reference standard likely to correctly classify the target condition (pulmonary tuberculosis)?

We answered 'yes' if a study used any of the solid or automated liquid culture methods or a combination of these methods. We answered 'no' if the study did not use culture methods or a clinical composite reference standard. We answered 'unclear' if we could not judge 'yes' or 'no'.

Applicability (3.4b): are there concerns that the target condition, as defined by the reference standard, does not match the question?

We judged 'low' if treatment was initiated after diagnosing using the composite reference standard. We judged 'high' if treatment was not initiated after using the composite reference standard. We judged 'unclear' if we could not judge low or high concern based on the available information.

We removed signalling question 4.2: *Did all the participants receive a reference standard?*

Statistical analysis and data synthesis

Due to the paucity of data, we did not perform a meta-analysis, investigate the heterogeneity (by smear status, setting, and tuberculosis burden), or perform sensitivity analysis as specified in the protocol. We also could not perform analysis to fulfil our secondary objectives of comparing test accuracy due to limited data.