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Value of urine-based lipoarabinomannan (LAM) antigen tests for diagnosing tuberculosis in children: systematic review and meta-analysis

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ABSTRACT

Background: Tuberculosis (TB) is a global burden, and this is likely to remain the case due to a lack of adequate and accurate point-of-care diagnostic tests. Obtaining good-quality sputum from the bottom of the respiratory tract of children is challenging. Lipoarabinomannan (LAM) is a specific component of the mycobacterial cell envelope that is excreted in the urine of people with active TB. This study aimed to assess the performance of different types of urine-based LAM antigen tests for the diagnosis of TB in children.

Methods: Relevant databases were searched for studies that used urine-based LAM tests to diagnose TB in children. Study quality was assessed using the Joanna Briggs Institute Critical Appraisal Tool. Pooled sensitivity and specificity were calculated using the random-effect model in STATA Version 16.0. Moreover, subgroup analysis was undertaken to hinder the heterogeneity of the studies.

Results: Eleven articles were included in the final systematic review and meta-analysis. The pooled sensitivity and specificity of the *Mycobacterium tuberculosis* enzyme-linked immunosorbent assay (MTB-LAM-ELISA), Alere Determine TB LAM Ag (Alere LAM) test and the Fujifilm SILVAMP TB LAM (Fuji LAM) test in children aged <15 years with TB were 16.0% [95% confidence interval (CI) 10.25–42.25] and 95.61% (95% CI 93.74–97.74); 45.90% (95% CI 40.40–51.40) and 80.42% (95% CI 69.39–91.46); and 52.32% (95% CI 35.03–69.62) and 89.37% (95% CI 82.88–95.86), respectively. Subgroup analysis revealed that the pooled sensitivity and specificity of MTB-LAM-ELISA, Alere LAM test and Fuji LAM test were 33.5% (95% CI 34.86–100) and 95.83% (95% CI 91.50–100); 46.59% (95% CI 32.98–60.19) and 76.45% (95% CI 57.07–95.82); and 57.89% (95% CI 48.44–67.35%) and 87.66% (95% CI 75.29–100), respectively, in human immunodeficiency virus (HIV)-positive children; and 3.35% (95% CI 1.61–8.31) and 96.0% (95% CI 93.88–98.11); 32.33% (95% CI 7.63–57.03) and 79.07% (95% CI 62.62–95.51); and 50.95% (95% CI 27.45–74.45) and 89.47% (95% CI 84.72–94.22), respectively, in HIV-negative children.

Conclusion: The Fuji LAM and Alere LAM tests may be useful for the diagnosis of TB in children in conjunction with other more sensitive and specific tests, although a prospective study in relevant clinical settings is needed to evaluate this. There is a need for more evidence-based data on the use of these rapid diagnostic tools to diagnose TB in children independent of HIV status.

Background

Tuberculosis (TB) is a major public health problem globally. It is caused by the bacteria *Mycobacterium tuberculosis* (López and de Oca, 2012). TB can affect anyone, regardless of age or sex. Before the coronavirus disease 2019 (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent. In 2020, an estimated 9.9 million people (95% uncertainty interval 8.9–11 million) had TB. In this year, there were 1.3 million TB deaths among human immunodeficiency virus (HIV)-negative people and 214,000 deaths among HIV-positive people. However, there was a 21% decline in TB preventive treatment globally. Children accounted for 11% of the global TB burden in 2020. Globally, 1.4 million children were treated for TB between 2018 and 2020 (World Health Organization, 2021a).

The most common type of TB in children is pulmonary TB (Velayati et al., 2016). A diagnosis of TB in a child relies on careful assessment based on history of exposure, clinical examination and relevant diagnosis (World Health Organization, 2014). A diagnosis of pulmonary TB is commonly based on clinical symptoms, chest X-ray, microbiological examination using sputum microscopy, and culture.

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However, accurate diagnosis of TB in children is difficult. As such, the World Health Organization (WHO) endorsed various fast diagnostic methods to detect TB using urine samples (Iskandar et al., 2017). In sub-Saharan Africa, the TB epidemic is fuelled by widespread immunocompromised status resulting from the HIV epidemic (Corbett et al., 2003). The diagnosis of childhood TB is complicated by the absence of a practical gold standard. In childhood TB, smear microscopy positivity and culture yield are low, at <10–15% and <30–40%, respectively (Starke, 2003).

Over the last two decades, there have been significant advances in the field of TB diagnostics. However, the high cost and sophisticated infrastructure requirements represent major challenges, which affect implementation in many countries (Pai et al., 2006). In developing countries, the high cost and poor performance (poor sensitivity and specificity) of various diagnostic tests make the diagnosis of TB difficult (World Health Organization, 2011).

Accurate, reliable and rapid diagnostic methods and appropriate treatment are needed to reduce TB transmission, mortality and drug resistance (Uys et al., 2009). Several methods of TB diagnosis have been endorsed by WHO, but each method has advantages and disadvantages (World Health Organization, 2021b).

Obtaining good-quality sputum from the bottom of the respiratory tract of children is challenging. Sputum induction and gastric lavage are effective, but require well-trained staff and certain equipment (Marais et al., 2014). In children, T-cell and interleukin-12 responses are weaker compared with adults, which helps TB to disseminate easily among children. This increases the probability of detecting mycobacterial antigen in urine (Gervassi and Horton, 2014). The sensitivity of urinary mycobacterial lipoarabinomannan (LAM) detection differs with age, and is higher in TB patients co-infected with HIV (Lawn, 2012).

LAM is a specific component of the mycobacterial cell envelope that is excreted in urine. The detection of LAM has been endorsed as a diagnostic tool by WHO, and enzyme-linked immunosorbent assays (ELISA) and lateral flow assays are commercially available (Whitelaw and Sturm, 2010). During *M. tuberculosis* infection, LAM exists in various body fluids; therefore, it can be an ideal candidate biomarker for the detection of *M. tuberculosis* (Flores et al., 2021). In recent years, novel urine-based LAM antigen detection technology has been developed, including the Fujifilm SILVAMP TB LAM (Fuji LAM) test and the Alere Determine TB LAM Ag (Alere LAM) test (Bulterys et al., 2019).

Inadequate TB diagnostics are a major hurdle in the reduction of disease burden, and accurate point-of-care tests are needed urgently. The aim of the present study was to assess the performance of different urine-based LAM antigen tests for the diagnosis of TB in children.

Methods

Literature search

Systematic literature searches of PubMed, EMBASE and Google Scholar databases were undertaken to assess the value of urine-based LAM antigen tests for diagnosing TB in children. This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist (Page et al., 2021) (Table S1, see online supplementary material). As this study was based on published primary studies, no ethical clearance was required. The following key words were used to extract the intended data: 'tuberculosis', 'TB', 'childhood TB', 'pediatric TB', 'Fujifilm SILVAMP TB LAM', 'Alere Determine^{TM} TB LAM Ag test', 'MTB ELISA Test (Alere)', 'lipoarabinomannan (LAM)', 'sensitivity' and 'specificity' (Table S2, see online supplementary material). The search terms and their variations were used in combination. The Boolean operators AND and OR were used accordingly. Articles were limited to papers published in the English language, without limits on the year of publication. The final search was performed on 15 January 2022.

Selection criteria

The included articles were peer-reviewed, met the inclusion criteria, and addressed the study objective adequately. Two authors (GS and AA) selected articles based on their title and abstract. Additionally, they performed independent screening of the full text of the retrieved articles. The inclusion criteria were as follows: (i) English language; (ii) reports the sensitivity and specificity of a urine-based LAM test in children; (iii) conducted in Africa; and (iv) provides sufficient data on the Fuji LAM test and/or the Alere LAM test.

Systematic reviews and meta-analyses, reviews and abstract-only studies were excluded, as were studies of unsatisfactory quality.

Data extraction

A pre-designed Microsoft 2010 Excel data extraction sheet was used to collect relevant data from each eligible study. Two authors (GS and BD) performed the extraction activity. A third author (TT) subsequently checked the quality and completeness of the extracted data. The following information was extracted: first author's name; year of publication; study site; study period; age of participants; study design; sample size of participants and control groups (if available); proportion of patients with HIV; diagnostic method; and sensitivity and specificity with 95% confidence intervals (CI). All sensitivity and specificity data were extracted according to a microbiological reference standard.

Study definition

The Alere LAM test is an immunochromatographic test for the qualitative detection of LAM antigen of mycobacteria in human urine. The Fuji LAM test, a lateral flow test to detect LAM in urine, is a novel non-sputum-based point-of-care test. Children were defined as individuals aged <18 years.

Quality assessment

The quality of eligible articles was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool (Whiting et al., 2011). The JBI checklist for diagnostic test accuracy consists of 10 quality indicators. These quality indicators were turned into 100%, and a score >80% was classed as high quality, 60–80% was classed as medium quality, and was classed as <60% low quality. The quality assessment was carried out by two authors (GS and TT), and the difference between the two assessors was managed by a third author (AA).

Data analysis

Data were summarized and saved in Microsoft Excel 2016 before being exported into STATA Version 16.0 for analysis. Pooled sensitivity and specificity for each method were estimated with 95% confidence intervals (CI) using a random-effect meta-analysis model. Heterogeneity among studies was examined using Forest plots and I^2 heterogeneity tests. In the current review, I^2>50% a random-effect model was used for analysis. Presence of publication bias was assessed using funnel plot and egger's test (P-value=0.1). The Forest plots provide a visual inspection of the CI of effect sizes of individual studies. The presence of non-overlapping intervals suggests heterogeneity.

Results

Study selection

Initially, 23 studies were identified through systematic searches of various electronic databases. Nine studies were excluded because they were duplicates. Two studies were excluded based on review of their

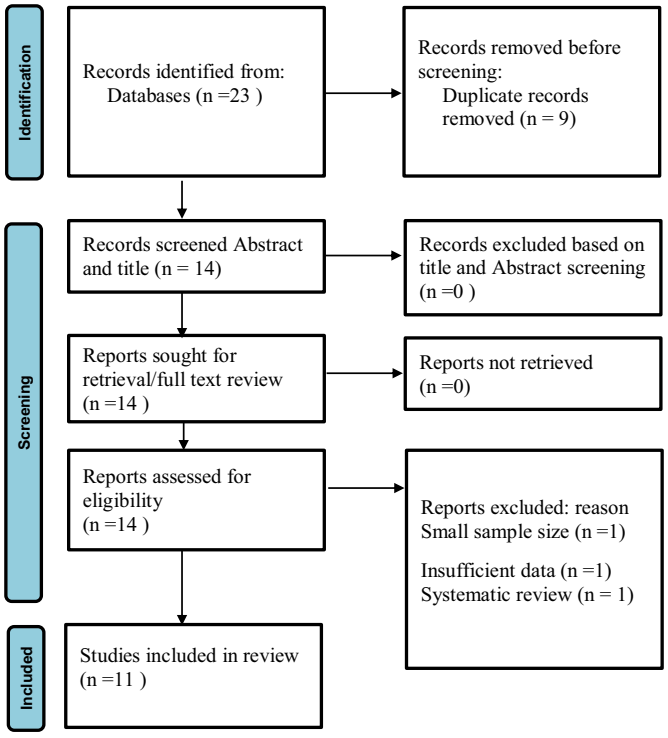

Figure 1. PRISMA flow diagram describing the selection of studies for this systematic review and meta-analysis.

titles and abstracts, and one study was excluded after a full-text review. Eleven studies met the inclusion criteria, and were included in this systematic review and meta-analysis (Blok et al., 2014; Nicol et al., 2014, 2021; Kroidl et al., 2015; LaCourse et al., 2018; Gautam et al., 2019; Nkereuwem et al., 2020; Comella-Del-Barrio et al., 2021; Dulce-Vasco et al., 2021; Schramm et al., 2021; Orikiriza et al., 2021) (Figure 1). All included studies had high-quality assessment scores based on the JBI assessment checklist for diagnostic test accuracy (Table S3, see online supplementary material).

Study characteristics

From the 11 studies included in this systematic review and meta-analysis, two were prospective observational studies (Nicol et al., 2014; Kroidl et al., 2015), eight were cross-sectional studies (Blok et al., 2014; LaCourse et al., 2018; Gautam et al., 2019; Nkereuwem et al., 2020; Dulce-Vasco et al., 2021; Nicol et al., 2021; Orikiriza et al., 2021; Schramm et al., 2021) and one was a retrospective study (Comella-Del-Barrio et al., 2021). Among them, one study reported the diagnostic value of the Fuji LAM test in children with presumptive TB, while five studies reported the diagnostic value of the Alere LAM test and two studies reported the diagnostic value of both the Alere LAM test and the Fuji LAM test. Publication year ranged from 2014 to 2021. Only one study (Comella-Del-Barrio et al., 2021) was undertaken outside Africa. The age range for the study participants was 6 weeks to 15 years. Nine of the included studies were conducted in Africa. In total, the 11 studies included 2167 children (Table 1).

Overall diagnostic accuracy

Nine, three and three studies evaluated the diagnostic accuracy of the Alere LAM test, MTB-LAM-ELISA and Fuji LAM test, respectively. The total numbers of participants in studies investigating the three types of test were 2076, 717 and 713 for the Alere LAM test, MTB-LAM-ELISA and Fuji LAM test, respectively. Pooled sensitivities of the Alere LAM test, MTB-LAM-ELISA and Fuji LAM test were 16.0% (95% CI 10.25–42.25), 45.90% (95% CI 40.40–51.40) and 52.32% (95% CI 35.03–69.62), respectively, compared with the microbiological reference standard. Overall specificities of the three types of test were 95.61% (95% CI 93.74–97.74), 80.42% (95% CI 69.39–91.46) and 89.37% (95% CI 82.88–95.86) for the Alere LAM test, MTB-LAM-ELISA and Fuji LAM test, respectively (Figure 2).

Diagnostic value of MTB-LAM-ELISA, Alere LAM test and Fuji LAM test in HIV-positive children

This meta-analysis found that sensitivity and specificity of the three urine-based LAM tests in HIV-positive children were 33.5% (95% CI

Table 1
Characteristics of included articles.

Author_year	Country	Study period	Study design	Participant age	Method used	Sample size
Inge et al., 2015	Tanzania	2008 to Nov,2010	prospective	6 weeks to 14 years	MTB-LAM-ELISA assay and Determine TB-LAM	132 children with suspected active TB
Patricia et al., 2021	Haiti	August 2015 and December 2016	retrospective	0 to 14 years & 5 to 8 years control	FujiLAM test	59 presumptive and 20 control
Birgit et al., 2021	Niger	February to August 2016,	cross-sectional	<5 years old	Alere Determine™ TB LAM Ag test	102 SAM TB Presumptive &100 non presumptive <5 child
Blok et al., 2014	south Africa	June 2011to February 2012	cross-sectional	3 months and 13 years	Clearview TB ELISA(Alere)	50 children suspected meningitis TB
Osorio et al., 2020	Mozambique	1 February to 31 August 2018.	cross-sectional	0–59 months	Alere Determine TB LAM Ag	45 SAM presumptive TB
Esin et al., 2020	Gambia,Mali, Nigeria, and Tanzania	July 1, 2017, to Dec 1, 2018,	cross-sectional	< 15 years	FujiLAM and Alere LAM testing	415 presumptive
Mark et al., 2014	S/africa	March 1, 2009, to April 30, 2012	prospective observational	15 years or younger	Alere lateral flow and Alere ELISA	535 presumptive
Mark et al., 2021	South Africa,	01/9/2016 to 17 /9/2018.	cross-sectional	<15 years	Alere LAM and FuijLAM	202 presumptive & 17 HIV-TB pos
Sylvia et al., 2018	Kenya	April 2013 to May 2015	cross-sectional	≤12 years	AlereDetermine™ TB LAM Ag Test	129 HIV pos
Guatam et al., 2019	India		cross-sectional	1–14-years	Alere Determinee TB LAM Ag	280 suspicion of intrathoracic TB and 101 lymph node TB
Patrick et al., 2021	Uganda		crossectional	<2 years	AlereLAM	219

ELISA, enzyme-linked immunosorbent assay; Fuji LAM, Fujifilm SILVAMP TB lipoarabinomannan test; Alere LAM, Alere Determine TB lipoarabinomannan Ag test; TB, tuberculosis.

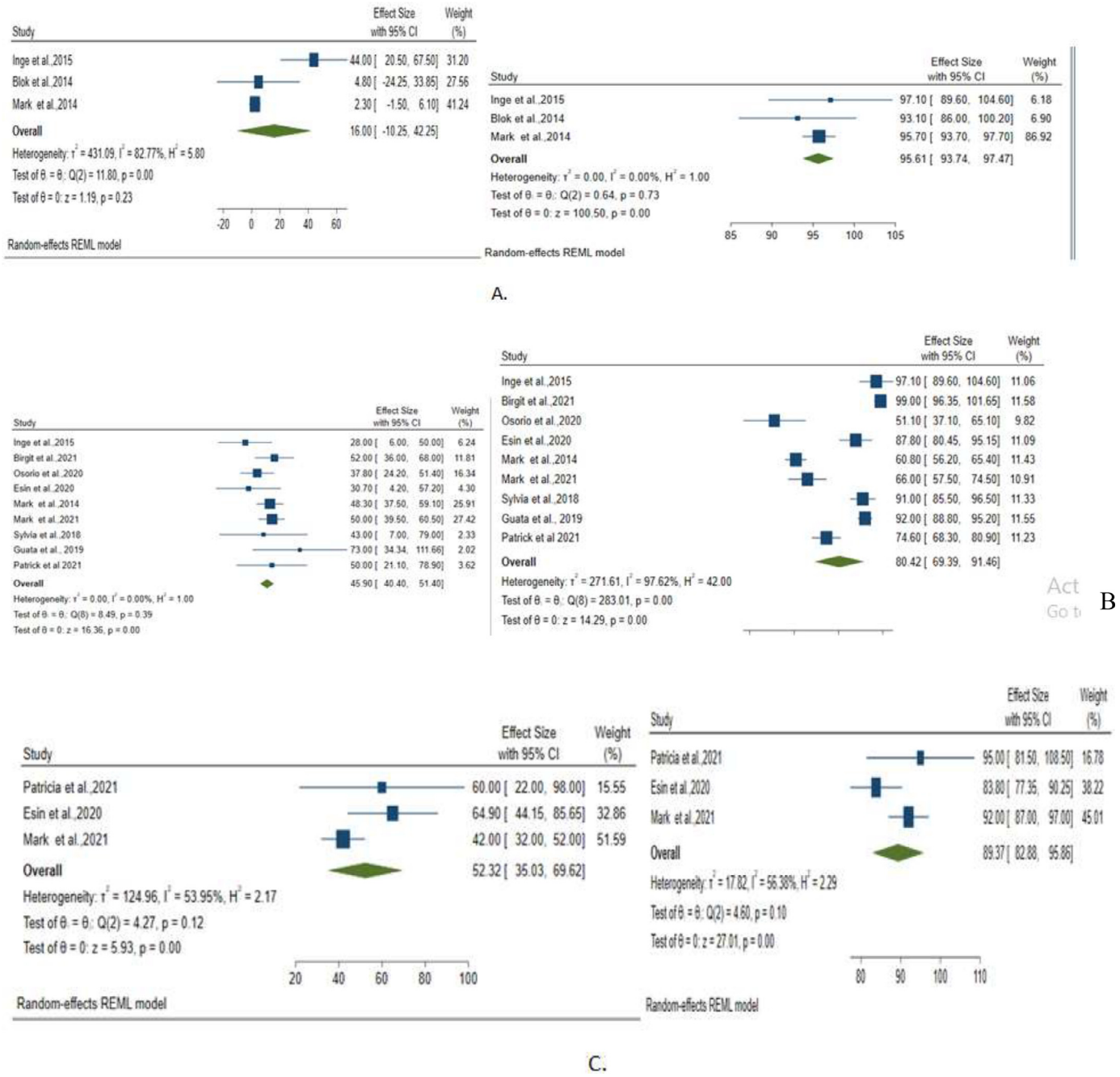

Figure 2. Overall pooled sensitivity and specificity of urine-based lipoarabinominan (LAM) tests in children. (A) *Mycobacterium tuberculosis* enzyme-linked immunosorbent assay. (B) Alere Determine TB LAM Ag test. (C) Fujifilm SILVAMP TB LAM test.

34.86–100) and 95.83% (95% CI 91.50–100); 46.59% (95% CI 32.98–60.19) and 76.45% (95% CI 57.07–95.82); and 57.89% (95% CI 48.44–67.35%) and 87.66 (95% CI 75.29–100) for MTB-LAM-ELISA, Alere LAM test and Fuji LAM test, respectively. The Fuji LAM test had better sensitivity for HIV-positive children than the other two tests. However, MTB-LAM-ELISA had better specificity than the other two diagnostic tools (Figure 3).

Diagnostic value of MTB-LAM-ELISA, Alere LAM test and Fuji LAM test in HIV-negative children

Two studies on the MTB-LAM-ELISA, four studies on the Alere LAM test and three studies on the Fuji LAM test had data on the sensitivity and specificity of the tools in HIV-negative children. Pooled sensitivity and specificity for MTB-LAM-ELISA were 3.35% (95% CI 1.61–8.31) and 96.0% (95% CI 93.88–98.11), respectively. The respective values were 32.33% (95% CI 7.63–57.03) and 79.07% (95% CI 62.62–95.51) for the Alere LAM test, and 50.95% (95% CI 27.45–74.45) and 89.47% (95% CI 84.72–94.22) for the Fuji LAM test (Figure 4).

Diagnostic value of the Alere LAM test by age group in children

Two studies reported the sensitivity and specificity of the Alere LAM test among children by age group. Values were 70.13% (95% CI 53.65–86.61) and 69.17% (95% CI 35.28–100), respectively, among children

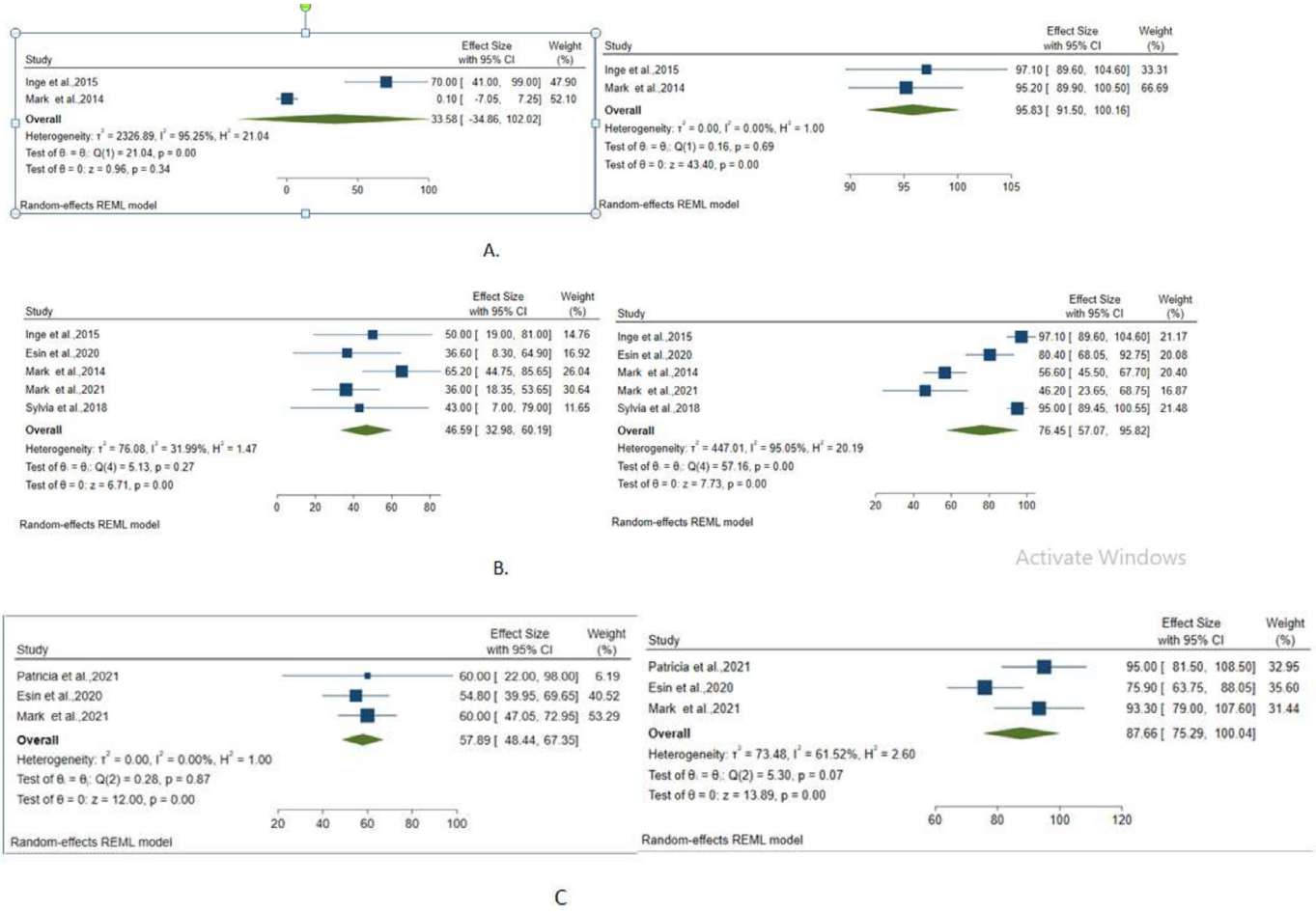

Figure 3. Pooled sensitivity and specificity of urine-based lipoarabinominan (LAM) tests in human-immunodeficiency-virus-positive children. (A) *Mycobacterium tuberculosis* enzyme-linked immunosorbent assay. (B) Alere Determine TB LAM Ag test. (C) Fujifilm SILVAMP TB LAM test.

aged <24 months, and 41.75% (95% CI 30.34–53.15) and 84.48% (95% CI 61.26–100) in children aged ≥24 months (Figure 5).

Discussion

The early diagnosis of TB is difficult, especially in children. There is a need for new diagnostic tests with high specificity and sensitivity, and a shorter turnaround time compared with the present diagnostic methods (Tsara et al., 2009). Urine-based LAM tests are recommended for immunocompromised HIV patients. Mycobacterium LAM tests use urine samples, which are easily available from any patient without age limits, to diagnose mycobacterium antigen (Alcorn et al., 2018). This systematic review and meta-analysis provides the diagnostic values of the Alere LAM test, MTB-LAM-ELISA and Fuji LAM test for the diagnosis of TB in children aged <15 years.

This review found that overall sensitivity of the Alere LAM test was comparable with the results from the WHO guideline (42%) for urine-based lateral flow LAM assays (World Health Organization, 2019). This finding implies that the Alere LAM test could be useful for identifying TB in children.

Without including other factors, the results of this review indicate that the Fuji LAM test had higher sensitivity and specificity than the Alere LAM test in children with presumptive TB. Sensitivity of the Fuji LAM test found in this review was similar to that reported in studies on HIV-negative adults with presumptive TB (53.2%) (Broger et al., 2020). Furthermore, the pooled sensitivity and specificity of the Fuji LAM test found in this review were similar to results reported in a previous paediatric study (Li et al., 2021).

MTB-LAM-ELISA showed higher specificity but lower sensitivity compared with the other two tests,. It is speculated that the antibody–antigen reaction in ELISA is less likely to be hindered by other factors than in lateral flow assays. The higher sensitivity and specificity of the Fuji LAM test may be due to the silver amplification method, which increases its sensitivity and specificity (Broger et al., 2019).

Sensitivity and specificity of the three tests were higher in HIV-positive children with presumptive TB compared with the general population of the same age. This finding supports the hypothesis that LAM is only shed into the urine of patients with active pulmonary TB in the context of glomerular dysfunction caused by HIV infection (Kroidl et al., 2015; Sigal et al., 2018). The lower specificity of the Alere LAM test and Fuji LAM test identified in this analysis is explained by the fact that the polyclonal antibodies used in the test could cross-react with urinary tract pathogens and fast-growing non-tuberculous mycobacteria, thus lowering their specificity (Kroidl et al., 2015; Sigal et al., 2018).

Additionally, in the case of HIV-negative children, it is hypothesized that the formation of immune complex, excess non-LAM protein in urine and other inhibitors masks the concentration of LAM in urine, such that it will be below the detection limit of the tests (De et al., 2015).LAM concentrations in urine can also be affected by bacterial burden, infection site and co-morbidities, such as HIV. The concentration of LAM was higher in patients co-infected with TB and HIV, and in patients with disseminated TB.

In this analysis, the sensitivity and specificity of the Fuji LAM test were proportional in HIV-negative and HIV-positive children with presumptive TB. This may be due to the high proportion of malnourished children in some of the studies included in this review.

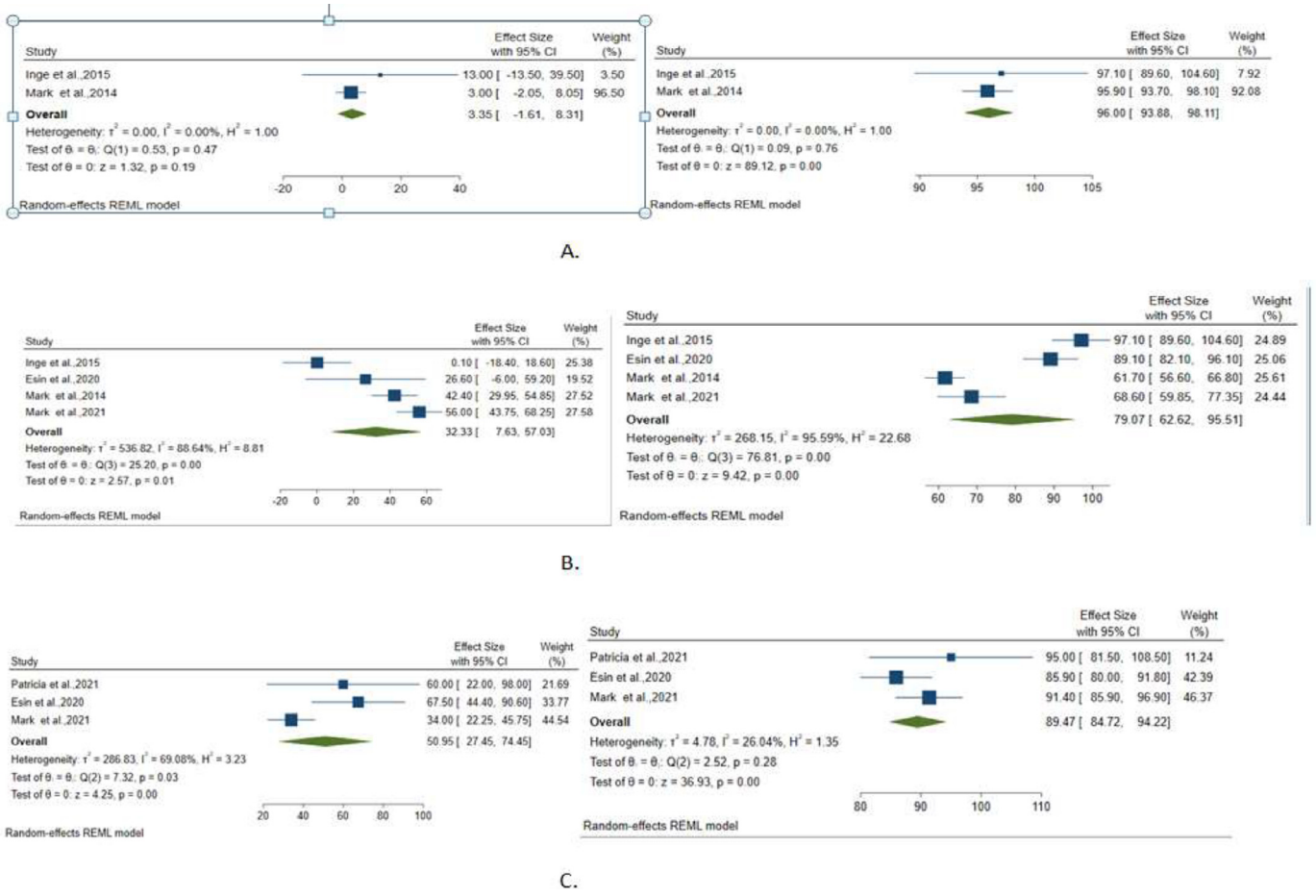

Figure 4. Pooled sensitivity and specificity of urine-based lipoarabinominan (LAM) tests in human-immunodeficiency-virus-negative children. (A) *Mycobacterium tuberculosis* enzyme-linked immunosorbent assay. (B) Alere Determine TB LAM Ag test. (C) Fujifilm SILVAMP TB LAM test.

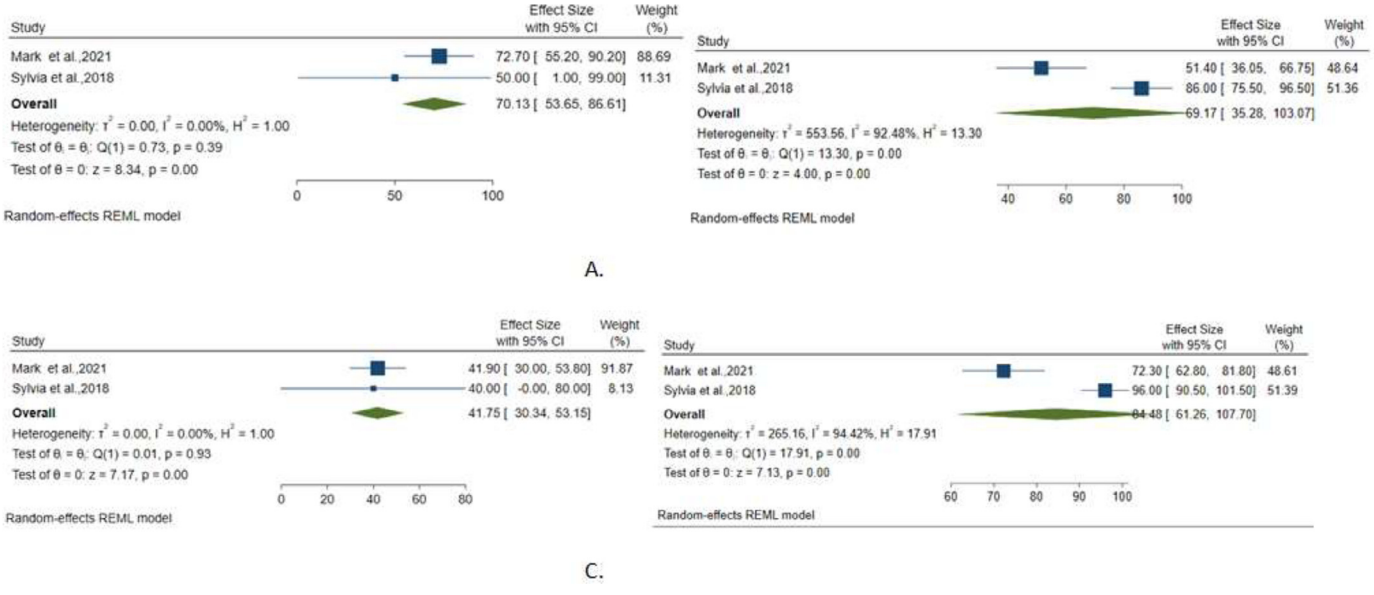

Figure 5. Sensitivity and specificity of the Alere Determine TB lipoarabinomannan Ag test in children aged (A) <24 months and (B) ≥24 months.

This meta-analysis found that the sensitivity of the Fuji LAM test for the diagnosis of childhood TB was low to moderate, and the specificity was high. Both specificity and sensitivity were lower in children than in adults infected with HIV (Chatla et al., 2021). Sensitivity of the Alere LAM test in this review was comparable with that found in reports from HIV-positive adults (42%) (Bulterys et al., 2019).

In this study, the sensitivity and specificity of the Alere LAM test were higher in children aged <24 months compared with those aged ≥24 months. This result was in advance of the conclusions of a previous study that age range, malnutrition, and positive acid-fast bacilli and culture results were predictive of positive urine LAM (Iskandar et al., 2017).

Study limitations

First, there are few primary studies on urine-based LAM tests (MTB-LAM-ELISA, Alere LAM test and Fuji LAM test) in children, and only one study in this review was not from Africa, which may have led to bias. Second, as few data were available for inclusion in this review, it is difficult to conclude the test performance in children, but the results may be used as baseline data. Third, there was heterogeneity among the studies, which indicates that interpretation of the results needs attention.

Conclusions

The Fuji LAM test and Alere LAM test may be useful for the diagnosis of TB in children in conjunction with other more sensitive and specific tests, although prospective studies in relevant clinical settings are needed to evaluate this. Although urine LAM assays have low sensitivity and specificity, their ease of use makes them useful as an add-on test in highly malnourished children. There is a need for more evidence-based data on the use of these rapid diagnostic tools for the diagnosis of TB in children independent of HIV status.

Data availability

Data are available on request from the corresponding author.

Authors' contributions

Getachew Seid: conceptualization, data extraction and analysis, review manuscript. **Ayinalem Alemu**: review manuscript, data extraction and analysis. **Tsegaye Tsedalu**: review manuscript, data extraction and analysis. **Biniyam Dagne**: data extraction, review manuscript.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2022.06.004.

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