

# Variable Diagnostic Performance of Stool Xpert in Pediatric Tuberculosis: A Systematic Review and Meta-analysis

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**Background.** Difficult specimen collection and low bacillary load make microbiological confirmation of tuberculosis (TB) in children challenging. In this study, we conducted a systematic review and meta-analysis to assess the diagnostic accuracy of Xpert on stool for pediatric tuberculosis.

**Methods.** Our search included studies from 2011 through 2019, and specific search terms were used to retrieve articles from Pubmed, EMBASE, BIOSIS, ClinicalTrials.gov, and Google Scholar. Risk of bias was assessed using the QUADAS 2 tool. The protocol was registered in PROSPERO (CRD42018083637). Summary estimates of sensitivity and specificity were conducted using meta-disc Software assuming a random-effects model.

**Results.** We identified 12 eligible studies, which included data from 2177 children, of whom 295 (13.6%) had bacteriologically confirmed TB on respiratory specimens. The pooled sensitivity of Xpert MTB/RIF on stool specimens compared with bacteriologically confirmed tuberculosis with respiratory specimens was 0.50 (95% CI, 0.44–0.56) with an  $I^2$  of 86%, which was statistically significant ( $P < .001$ ). The pooled specificity was 0.99 (95% CI, 0.98–0.99;  $I^2 = 0.0\%$ ;  $P = .44$ ).

**Conclusions.** Despite the observed heterogeneity, stool may be considered an additional specimen to support diagnosis of pulmonary TB in children, especially in settings where it is impossible to get respiratory samples. Further studies should evaluate its optimization as a diagnostic tool.

**Keywords.** children; fecal; GeneXpert; MTB/RIF.

In 2019, around 10.0 million people developed TB disease, of whom 12% were children <15 years of age [1]. These statistics are considered an underestimation, as a lot of pediatric cases with TB disease are missed due to limited diagnostic capabilities and underreporting in high-burden settings [2].

The diagnosis of pulmonary TB (PTB) in children remains a challenge, especially in the highest-risk children <5 years of age [3, 4]. PTB in children is often paucibacillary, and young children are unable to expectorate sputum, which necessitates using invasive procedures for specimen collection [5–8]. The usual method is collection of early morning gastric aspirates, which requires placement of a nasogastric tube for collection and fasting [9]. In addition, once a specimen is collected, a long incubation time (3–4 weeks) is often required to isolate the *Mycobacterium tuberculosis* on culture, which limits making a

timely diagnosis and leads to delays in treatment initiation [10]. This is especially problematic in children aged <5 years, who are at highest risk for the development of tuberculous meningitis and miliary tuberculosis [2]. Most children in high-burden, low-resource settings are diagnosed with and treated for TB based on clinical symptoms, epidemiologic risk, chest radiograph findings, and, if available, tuberculin skin testing [11, 12]. This contributes to both underdiagnosing and overtreatment of childhood TB, especially in young children [7].

Improving the diagnostic accuracy of PTB in children is important to better define the burden of childhood TB worldwide and to provide effective treatment to those with a true diagnosis [13]. Although other diagnostic tools including clinical scoring systems, chest radiographs, and tuberculin skin tests support TB diagnosis in children, they are often unreliable and insensitive, especially in children with HIV [14]. There have been several recent advancements in specimen collection and the use of rapid molecular testing that have improved the microbiologic yield and diagnosis of TB in children. Sputum induction and nasopharyngeal aspirate are less invasive [15]. The sensitivity of Xpert MTB/RIF compared with culture on induced sputum specimens in children has been reported to be 66% with a specificity of 98% [16]. Despite these advances, a number of children with tuberculosis are still missed.

More recently, studies have evaluated the use of Xpert MTB/RIF on nontraditional specimens such as urine and stool, which

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bear a special advantage of ease of collection, for the diagnosis of pediatric TB [5–7, 12]. This study aims to systematically review and conduct a meta-analysis of the current literature evaluating the diagnostic accuracy of Xpert MTB/RIF on fecal specimens compared with respiratory specimens to diagnose pulmonary TB in children.

## METHODS

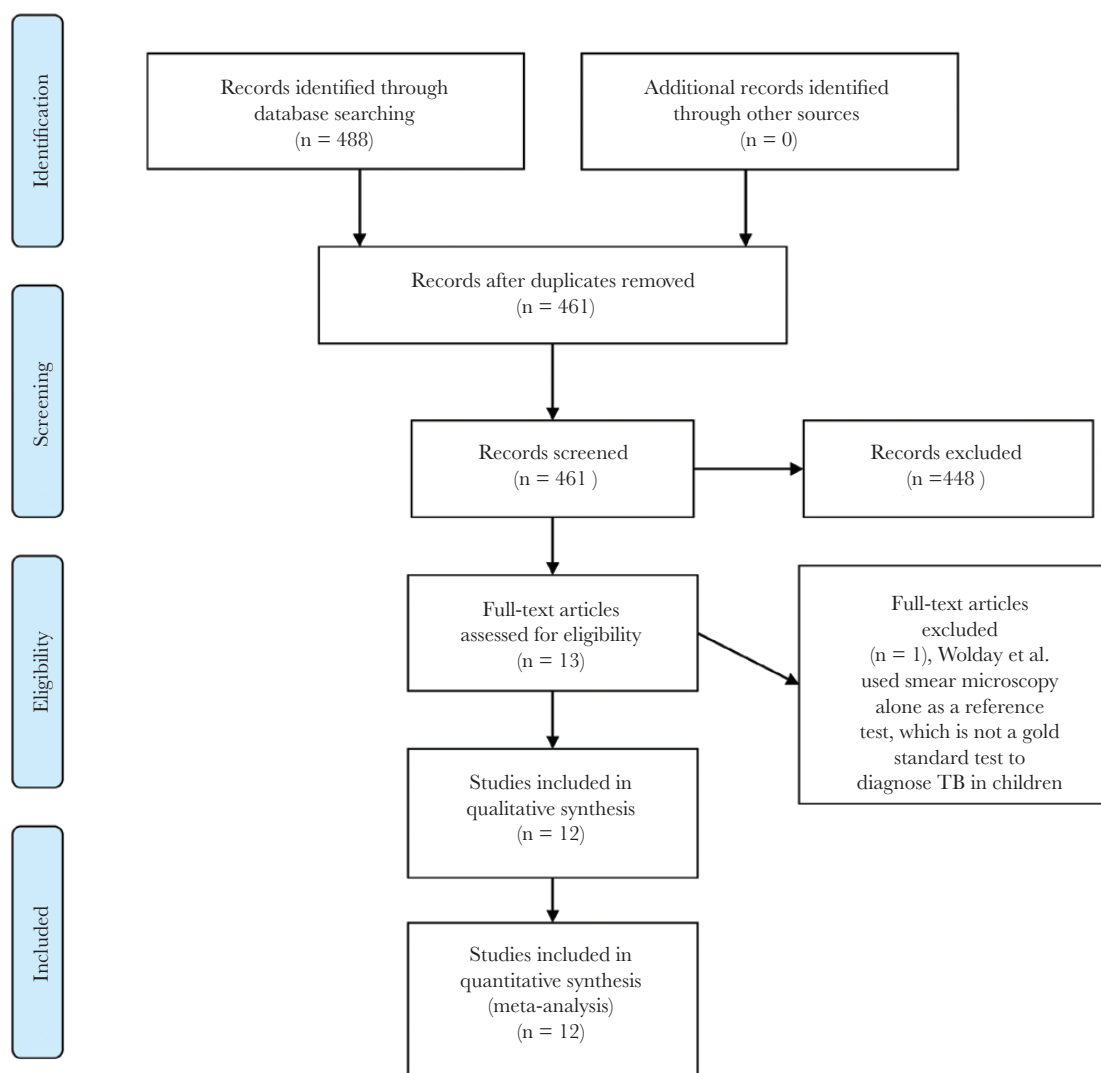
### Search Strategy

We used PubMed, Google Scholar, EMBASE, and BIOSIS to systematically search the published literature. We also looked at ClinicalTrials.gov to find ongoing trials. Wider and specific medical subject heading (MESH) terms were used as search strings. We used key words including Xpert, Gene Xpert, Xpert MTB/RIF assay, stool, feces, pediatrics, children, and tuberculosis in various combinations. We tried to identify additional

studies from conference proceedings and through discussions with childhood TB experts and researchers. When needed, we communicated with corresponding authors to request additional study information. Our last search occurred on February 15, 2019.

### Study Eligibility Screening

Inclusion criteria were predefined in the context of the research question. We included studies involving children aged  $\leq 16$  years, that were reported in English after January 1, 2011, that assessed the diagnostic accuracy of Xpert MTB/RIF assay on stool specimens (index test) in comparison with bacteriologically confirmed TB on a respiratory specimen, defined as culture, Xpert MTB/RIF assay, and/or smear microscopy on a gastric aspirate, expectorated/induced sputum, or nasopharyngeal aspirate as the reference standard. We did not restrict studies based on their setting or study design.



**Figure 1.** Selection of studies using the Preferred Reportable Items in Systematic Review and Meta-Analysis flow diagram.

Identified articles were screened and presented using the Preferred Reportable Items in Systematic Review and Meta-Analysis (PRISMA) flow diagram (Figure 1). Two of the authors (M.G. and L.H.C.) assessed the studies for eligibility, and any disagreement was resolved through discussion and involvement of a third author (L.W.). Thirteen studies met the inclusion criteria (Table 1). Following further review, 1 study was excluded as it used smear microscopy alone as a reference standard [17].

We reported the results following the PRISMA checklist (Supplementary Table 1).

### Assessment of Risk of Bias

Two authors (M.G. and L.W.) independently assessed each study for risk of bias using Quality Assessment for Diagnostic Accuracy Studies (QUADAS 2) tool. Disagreements between the reviewers' ratings were resolved through discussion. Summary of assessment of risk of bias was conducted using RevMan analysis software (version 5.3). In order to minimize publication bias, we attempted to retrieve all relevant unpublished studies through communication with experts in the field. The protocol was registered in PROSPERO (CRD42018083637).

### Data Extraction Techniques

Variables including year of study publication, study design, study population, study setting, types of specimen analyzed, diagnostic tests performed, amount of stool specimen processed, and bacteriologic results on respiratory and stool specimens (Table 1) were extracted independently by 2 reviewers (M.G. and L.W.).

### Statistical Analysis

Data extracted from included studies were entered into Review Manager (RevMan) (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration) and meta-disc software (version 1.4) for analyses [18]. Summary estimates with 95% confidence intervals were calculated to estimate the pooled sensitivity and specificity of Xpert MTB/RIF using a bivariate random-effects model. This model accounted for potential sources of variation within and across studies while calculating the summary estimates of sensitivity and specificity. The degree of study heterogeneity was calculated using  $I^2$ , and possible sources of study heterogeneity were explored through metaregression and subgroup analysis.

## RESULTS

We retrieved 448 published articles and identified 38 studies (Figure 1). Following review of titles and abstracts, 13 studies met our inclusion criteria. Despite meeting the inclusion criteria, following review of the full article, 1 study was excluded, Wolday et al. [17], as the study used smear microscopy alone as a reference standard, which was not considered sufficient to validate the diagnostic accuracy of the Xpert MTB/RIF on stool

**Table 1. Features of Included Studies**

Author (Year)	Study Setting (Country)	Sample Size, No.	Age of Inclusion, Median, y	HIV Prevalence, %	Specimen Types and Amount	No. of Samples Collected per Child, Respiratory, Stool	Bacteriologically Confirmed TB in Respiratory Samples, No. (%)	Xpert MTB/RIF Positive Stool Specimen, No. (%)
Moussa (2016)	Hospital (Egypt)	115	1–15 y, NR	0	Expectorated/IS, stool (2 g)	2, 2	36 (31.3)	30 (26)
Banada (2016)	Hospital and outpatient clinic (South Africa)	40	<15 y, NR	Unknown	GA or IS, stool (0.2–1.2 g)	1, 1	20 (50)	17 (42.5)
Nicol (2013)	Hospital and outpatient clinic (South Africa)	115	<15 y, 2.6	14.8	IS, stool (0.15 g)	2, 1	17 (14.8)	8 (6.9)
Walters (2017)	Hospital (South Africa)	379	<13 y, 1.3	13.7	GA/sputum, IS, NPA, stool (1–4 g)	3, 1	73 (19.3)	23 (6.1)
Hasan (2017)	Hospital (Pakistan)	50	1–15 y, 6.8	Unknown	GA/sputum, stool (0.15 g)	1, 1	12 (24)	10 (20)
Marcy (2016)	Hospital (Burkina Faso, Cambodia, Vietnam)	281	≤13 y, 7.2	100	GA/sputum, NPA, string test, stool (0.5 g)	4–5, 1	29 (10.3)	18 (6.4)
La course (2018)	Hospital (Kenya)	165	≤12 y, 2	100	GA/sputum, stool (NR), urine LAM	2, 1	13 (7.9)	5 (3.4)
Chipinduro (2017)	Outpatient clinics (Zimbabwe)	222	5–16 y, 10.6	50.9	IS, stool (0.15 g)	1, 1	19 (8.6)	13 (5.9)
Di Nardo (2018)	Outpatient clinic (Swaziland)	38	<15 y, 6.5	52.5	IS/sputum, NPA, GA, stool (0.05 g)	2, 2	10 (26.3)	5 (13.2)
Walters (2018)	Hospital (South Africa)	280	NR, 1.3	12.5	IS/sputum, GA, stool (0.6 g)	1, 1–2	23 (8.2)	14 (5)
Orkirza (2018)	Hospital (Uganda)	392	1 mo–14 y, NR	31	IS/sputum, stool (NR)	2, 1	17 (4.3)	6 (1.5)
Memon (2018)	Outpatient clinic (India)	100	<15 y, 11	Unknown	IS, GA, stool (0.2 g)	2, 1	40 (40)	4 (4)

Abbreviations: GA, gastric aspirate; IS, induced sputum; MTB/RIF, *Mycobacterium tuberculosis*/rifampicin; NPA, nasopharyngeal aspirate; NR, not reported; TB, tuberculosis.

specimens. We included 1 study [19] that used stool PCR as a diagnostic tool as the both Xpert MTB RIF and PCR techniques involve DNA amplification.

All included studies were conducted in low- and middle-income settings (9 being among the 30 high-TB burden countries) and involved children from 0 to 16 years of age (Table 1). A total of 2177 participants were included in the analysis. Most studies collected more than 1 respiratory specimen (gastric aspirate, expectorated/induced sputum, and nasopharyngeal aspirate) per child (Table 1). One of the studies [20] used the string test in children >4 years of age. All studies used a positive Xpert MTB/RIF test or MTB culture or both tests on respiratory specimens as a reference standard (Table 1), except 1, which used Xpert MTB/RIF and/or MTB culture and/or smear microscopy [21].

Risk of bias assessment was evaluated using QUADAS 2 [22]. Risk of bias in the patient selection was rated as high in 2 studies, as 1 was a case-control study [7] and the other used convenience sampling [12]. Three studies were rated as having unclear risk, as they did not mention random or consecutive enrollment of participants or excluded important groups of patients [21, 23, 24]. As Xpert is an automated test, risk of bias regarding conduct of the index test was rated as low for all studies except 1, as it used an in-house qPCR. Risk of bias with respect to the reference standard was rated as low for all studies, as all used bacteriologically confirmed TB on respiratory samples as a reference standard, which is the current diagnostic modality with all its limitations. Patient flow and timing were rated as low risk of bias in all studies except 4, out of which 2 took stool samples within in 7 days of enrollment [25, 26], 1 took samples within 6 weeks of enrollment [19], and the other did the index test within 6 months of storage of samples. Applicability concern on patient selection was rated as high in 2 studies that involved

only HIV-infected children, as stool Xpert has a different performance in children, and a third study due to use of TB cases and noncases in their design. We rated applicability concern of index test as unclear in all studies due to diverse methods used in the absence of instruction from the manufacturer, whereas we rated 1 study as having high applicability concern as it used a qPCR test, which is not exactly the same as Xpert. We scored applicability concern with respect to reference standard as low in all studies, as all did the reference tests based on standardized methods (Figure 2; Supplementary Figure 1).

Out of the total 2177 patients, 295 (13.6%) had bacteriologically confirmed TB from respiratory specimens and ranged from 4.3% to 50%. The weighted sensitivity of stool Xpert MTB/RIF compared with bacteriologically confirmed tuberculosis on respiratory specimens (0.50; 95% CI, 0.44–0.56) varied considerably across studies (Figure 3A); however, the pooled specificity (0.99; 95% CI, 0.98–0.99) was highly consistent with an  $I^2$  of 0.0% (Figure 3B). A statistically significant ( $P < .001$ ) heterogeneity across studies was observed for sensitivity, as shown by an  $I^2$  of 86% (Figure 3A). We also ran a sensitivity analysis after excluding Di Nardo, as the study used an in-house PCR assay, and the sensitivity remained the same (Supplementary Figure 2).

A meta-regression using the number of respiratory and stool specimens collected and the amount of stool in grams as a covariate did not reveal a statistically significant association with the diagnostic accuracy of stool Xpert MTB/RIF. We did a subgroup analysis taking median age of 5 as a cutoff, which reduced the  $I^2$  to 37% ( $P = .19$ ) in studies with a median age <5, but the  $I^2$  remained high at 88.9% ( $P < .001$ ) in studies with a median age >5. The pooled sensitivity and specificity in those with median age <5 and >5 years were 0.39 (95% CI, 0.30–0.48) and 0.99 (95% CI, 0.98–1.00), and 0.45 (95% CI, 0.36–0.55) and 0.99 (95% CI,

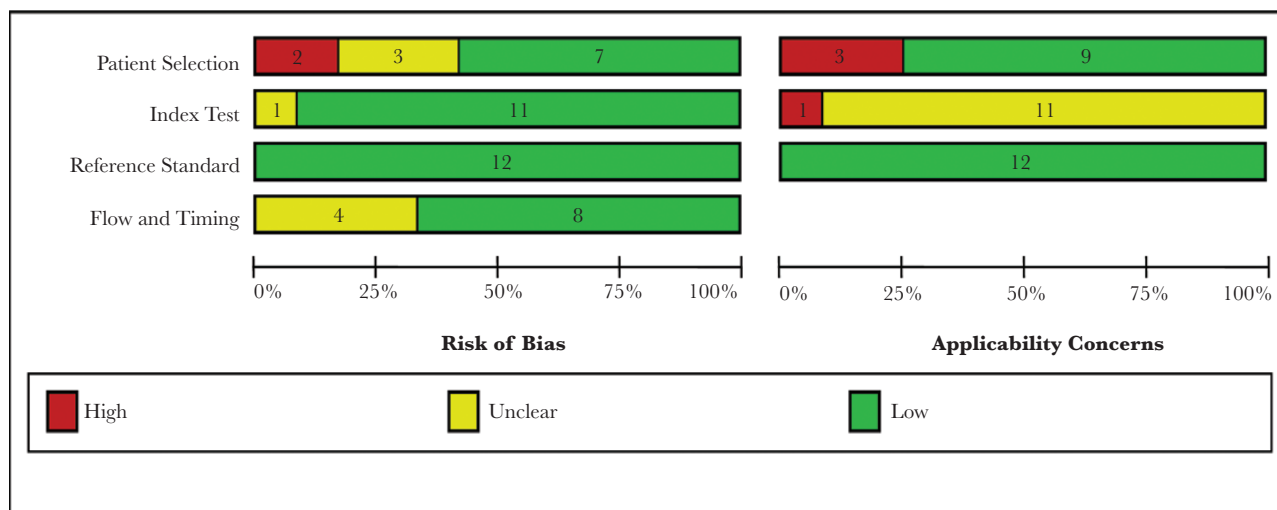
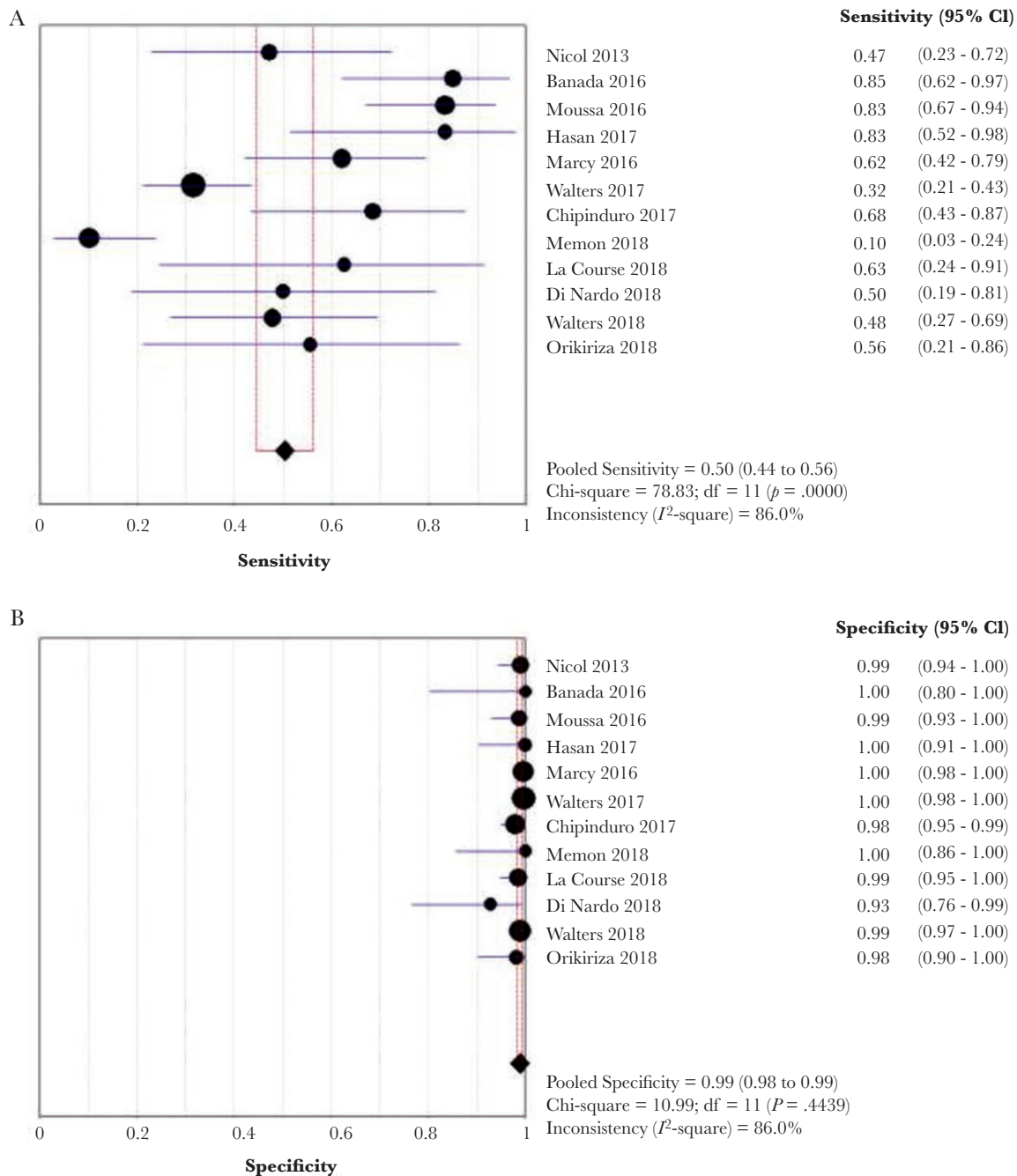


Figure 2. Summary of risk of bias assessment using QUADAS 2.



**Figure 3.** Forest plot for included studies showing the sensitivity (A) and specificity (B) of stool Xpert against bacteriologically confirmed tuberculosis.

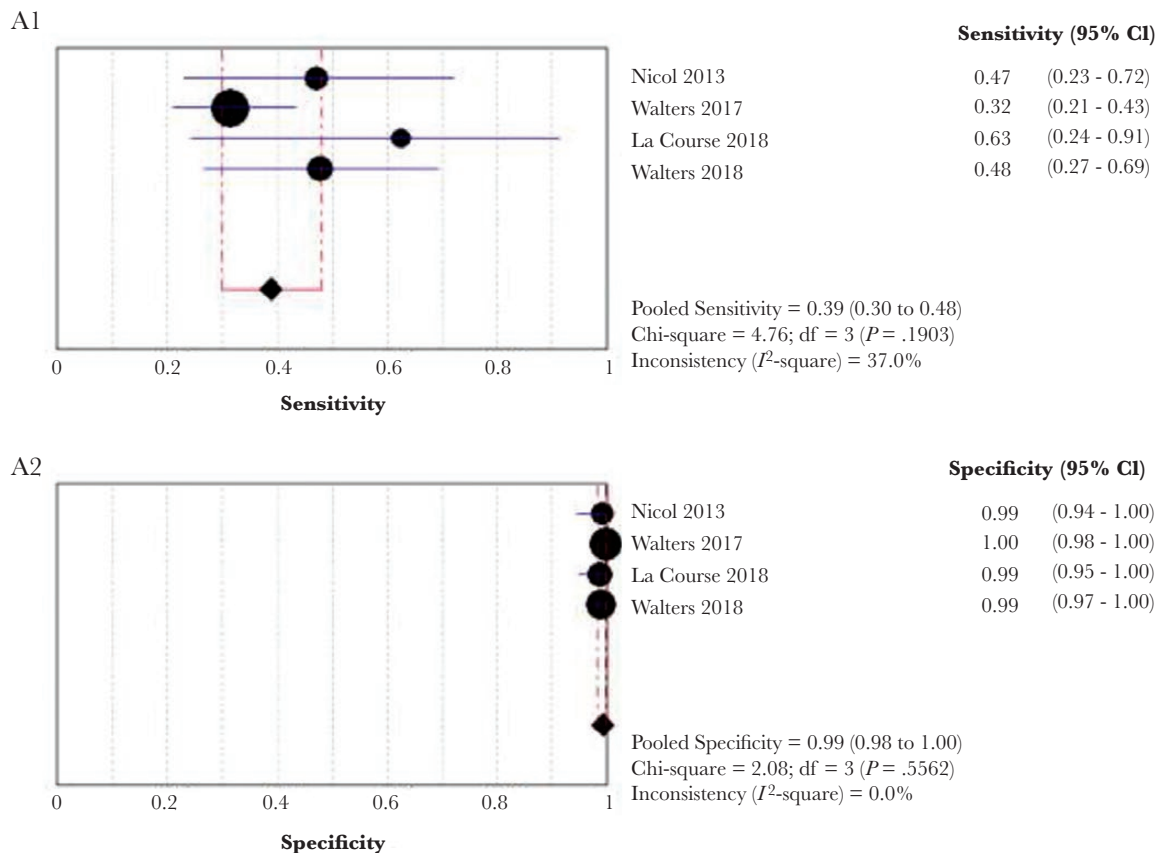
0.97–0.99), respectively (Figure 4A1, B1, A2, B2). Three studies did not report the median age of participants and were not included in the subgroup analysis. A further subgroup analysis that looked at the use of centrifugation for stool processing also revealed a pooled sensitivity of 0.68 (0.60–0.76) and 0.35 (0.29–0.43) for those with and without centrifugation, respectively (Figure 5A & B).

## DISCUSSION

Our analysis revealed that Xpert MTB/RIF on stool specimens has a pooled sensitivity of 50% (95% CI, 0.44–0.55) compared

with the reference standard of culture and/or Xpert on respiratory samples. In comparison with the pooled sensitivity of Xpert on respiratory specimens, our analysis revealed that stool Xpert MTB/RIF had lower sensitivity. The pooled sensitivities and specificities of Xpert MTB/RIF on expectorated or induced sputum specimens obtained from children with suspected TB were 62% (95% credible interval [CrI], 51%–73%) and 98% (95% CrI, 97%–99%), and 66% (95% CrI, 51%–81%) and 98% (95% CrI, 96%–99%), respectively [16]. With use of specimens from gastric lavage, Xpert’s sensitivity was 36%–44%





**Figure 4.** Subgroup analysis by median age <5 (A1 & A2) and >5 (B1 & B2).

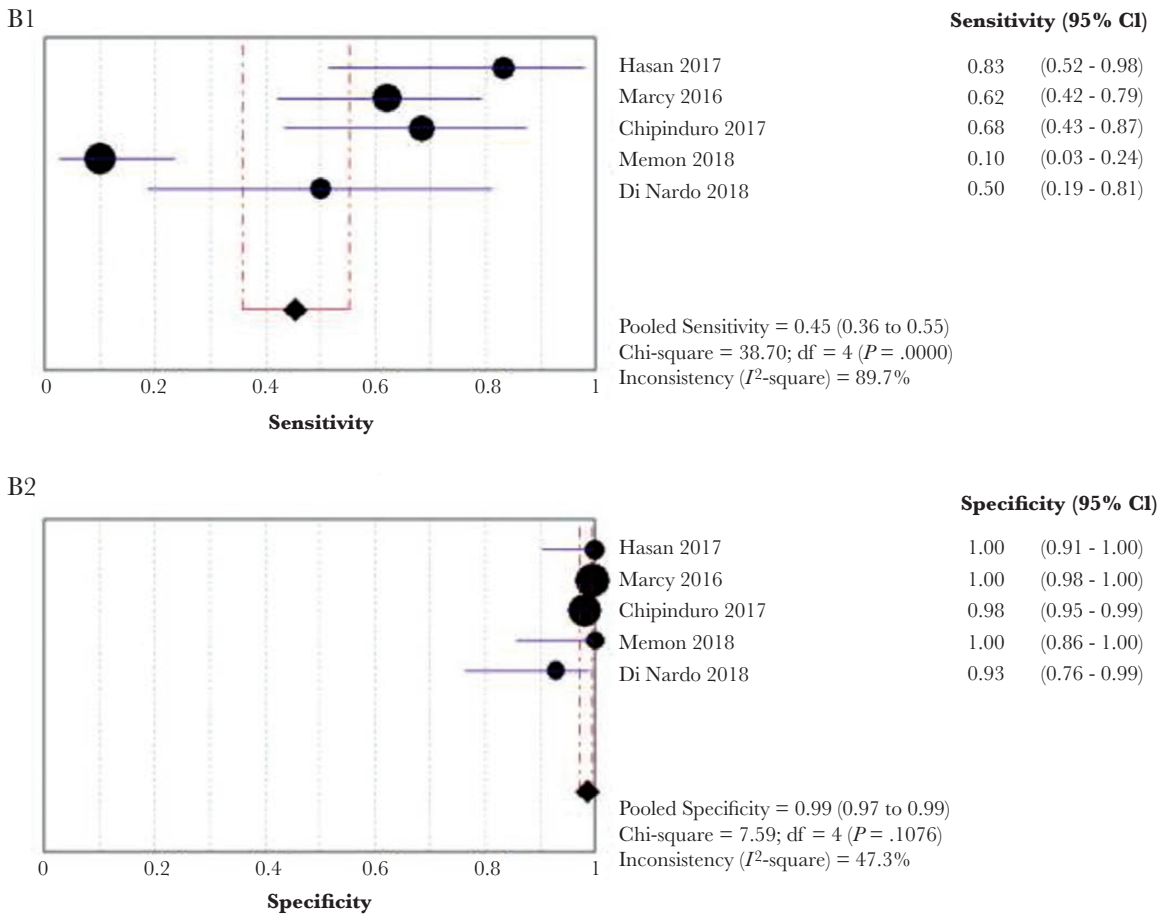
higher than the reported sensitivity for microscopy [16]. These studies contributed to the recommendation supporting the use of Xpert MTB/RIF on respiratory specimens for the diagnosis of TB in children [16]. Nevertheless, the specificity of stool Xpert was consistent and high across all the studies, with a pooled summary estimate of 0.99 (95% CI, 0.98–0.99). A recent meta-analysis on the diagnostic accuracy of stool Xpert by MacLean et al., which included 9 studies, showed a pooled sensitivity and specificity of 67% (95% CI, 52%–79%) and 99% (95% CI, 98%–99%), respectively, which is higher than ours, but with overlapping confidence intervals. However, they did not do subgroup analyses by age and other parameters due to the limited number of included studies [21, 27].

There was marked heterogeneity in the sensitivity reported across the included studies, ranging from 32% to 85%. Some of the studies took multiple respiratory specimens (up to 7 per child) [5, 6, 12, 19, 20, 23, 25, 26, 28] and used up to 3 reference tests, which included Xpert MTB/RIF and/or culture and/or smear microscopy [21], which may have lowered the sensitivity of Xpert MTB/RIF. Nevertheless, meta-regression to assess whether the number of stool or respiratory specimen taken per child could account for the heterogeneity was not statistically significant, calling for exploring for other possible factors. Another source of variation could be the difference in stool

specimen processing. As there is no instruction from the manufacturer regarding stool specimen processing for Xpert MTB/RIF testing, studies used a diverse method of specimen processing, which may have contributed to the reported inconsistent sensitivities. In order to explore more on the sample processing, we did a subgroup analysis based on use of centrifugation. The pooled sensitivity of studies with sample centrifugation showed a better sensitivity of 0.68 (0.60–0.76) compared with those without centrifugation 0.35 (0.28–0.43) (Figure 5A & B).

In spite of the World Health Organization’s recommendation to use Xpert on respiratory samples as a first-line diagnostic test for pediatric TB [29], practical implementation of methods to collect specimens in children unable to expectorate is still inadequate [30]. In 2012, 651 pediatric HIV sites were surveyed in Sub-Saharan Africa; only 6% had the capacity to collect induced sputum specimens, 5% had the capacity to do gastric aspirates, and only 2% were able to do NPA [30]. The limited capacity to implement specimen collection in children restricts the impact of the near point-of-care introduction of the Xpert assay [16, 30, 31], making stool Xpert MTB/RIF a good alternative despite having a modest sensitivity [23, 26, 28].

Though Xpert MTB/RIF on respiratory specimens has better sensitivity compared with stool specimens, the



**Figure 4.** Continued.

collection of respiratory specimens in young children is challenging, especially in primary care settings [30]. On the contrary, stool specimens are easy to collect and preclude aerosol-generating procedures [32]. Given their modest sensitivity, they can be used at primary health care levels if a better and simplified way of specimen processing with better sensitivity can be identified. Recently, a simplified method of sample processing was devised by KNCV, and stool Xpert using this method was able to identify 24 out of 27 children with positive respiratory samples, which is highly promising [33].

In addition, emerging evidence suggests that using larger specimen volumes and pretreating with stool processing buffer to inactivate PCR inhibitors achieve greater diagnostic yield of the stool Xpert MTB/RIF test [7]. Studies have also reported incremental sensitivity of repeat testing on stool from 44.4% to 70% [26]. Further studies are required to determine the optimal number of stool specimens per child, optimal specimen volumes, the need for a second specimen, and optimal and simple sample processing methods that increase sensitivity and make stool Xpert a point-of-care diagnostic test. Furthermore, the ongoing development of newer nucleic acid amplification tests

(NAATs) such as Xpert Ultra with an expected lower limit of detection could significantly impact the capacity to reach diagnostic confirmation [26].

## CONCLUSIONS

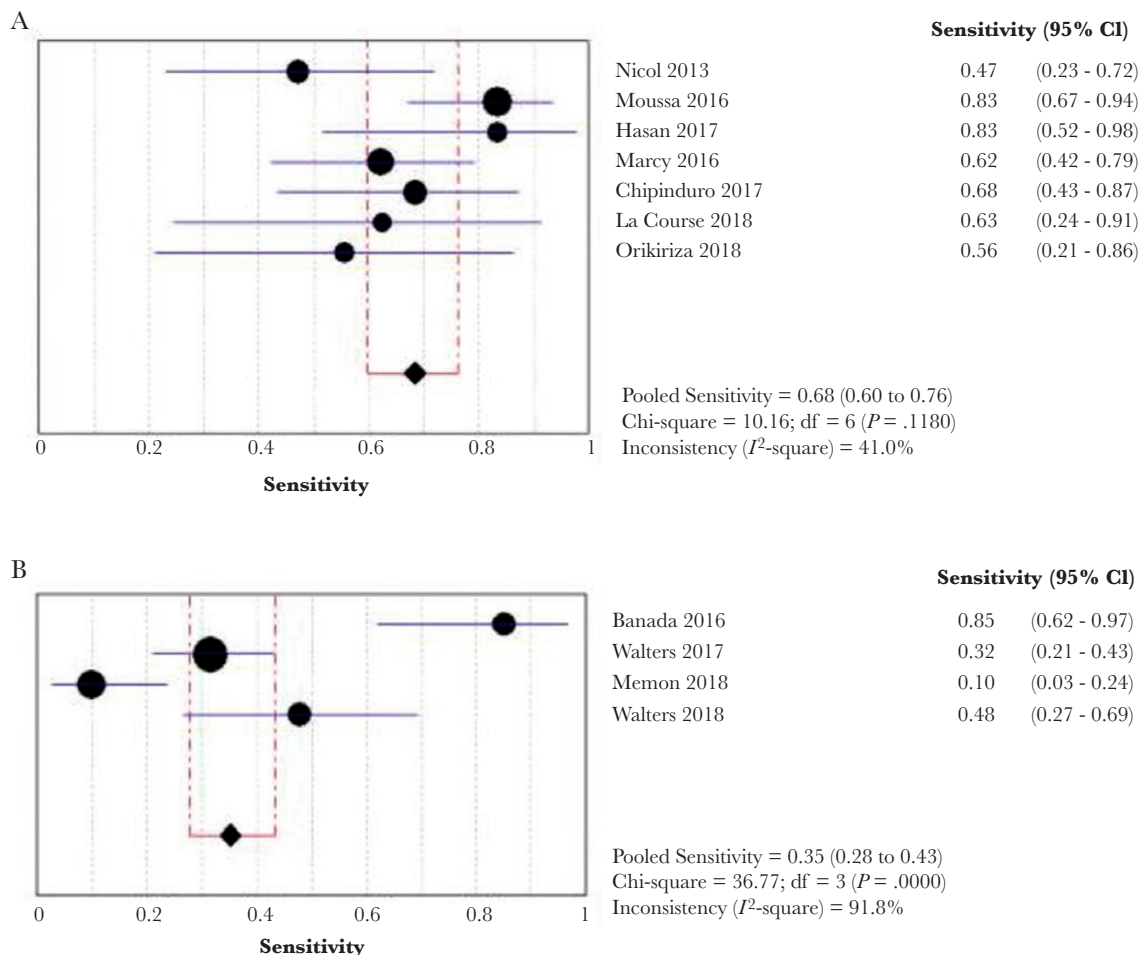
Overall, Xpert MTB/RIF testing of stool specimens could be considered an additional test to support the diagnosis of pulmonary TB in children, especially in settings where it is difficult to obtain respiratory samples. The ease of stool collection could allow for implementation as a point-of-care test at primary health care settings, especially if stool processing is optimized and standardized. This may improve time to diagnosis and minimize delay in the initiation of treatment.

## Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Figure 5.** Subgroup analysis by sample processing with centrifugation (A) and without centrifugation (B).

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**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Author contributions.** M.G. and L.W. were the originators of the research idea and did the literature search, L.H.C. & M.G. did the assessment of risk of bias, and L.W. and M.G. did the data extraction. Data analysis was done by M.G., Y.W., and G.T. All the authors reviewed and agreed to the final manuscript.

**Ethical approval.** The study was approved by the Emory Institutional Review Board and ALERT/AHRI Ethics Review Committee.

**Availability of data and materials.** The data we used for our analysis are from published studies that are publicly available.

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