Xpert MTB/RIF assay for diagnosis of extrapulmonary tuberculosis in children: A systematic review and meta-analysis

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Research article

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Abstract

Background: The Xpert® MTB/RIF assay (Xpert; Cepheid, Sunnyvale, CA, USA) is a cartridge-based nucleic acid amplification assay for rapid tuberculosis diagnosis and assessment of antibiotic sensitivity. Although previous evidence supports the use of Xpert for diagnosing extrapulmonary tuberculosis (EPTB) in adults, information regarding the accuracy of Xpert for EPTB only in children is lacking. This meta-analysis aimed to assess the accuracy of Xpert for detecting EPTB in children. Methods: We searched the MEDLINE, EMBASE, and the Cochrane Infectious Diseases Group Specialized Register from January 1, 2010, to July 16, 2019, for studies on diagnostic performance wherein Xpert was analyzed against cultures or composite reference standards for <18-year-old children with EPTB. Results: Exclusively on the basis of pediatric studies, 7 studies including 560 samples were selected. The pooled sensitivity and specificity of Xpert for all samples were 67% (95% CI 0.51-0.79) and 94% (95% CI 0.87-0.98), respectively. The area under the summary receiver operating characteristic (sROC) curve was 0.89. For lymph node tissues or aspirates, the pooled sensitivity and specificity of Xpert were 75% (95% CI 0.54-0.89) and 90% (95% CI 0.77-0.96), respectively; for cerebrospinal fluid (CSF), they were 40% (95% CI 0.23-0.60) and 96% (95% CI 0.85-0.99), respectively. Conclusion: Overall, Xpert displayed high specificity but modest specificity across various samples in the diagnosis of pediatric EPTB in comparison with the composite reference standard. Xpert sensitivity varied with the sampling site, and was especially lower for CSF samples. Positive Xpert results may be considered to indicate a presumptive case of pediatric EPTB, whereas negative test results indicate that the possibility of pediatric EPTB should not be excluded.

Background

Extrapulmonary tuberculosis (EPTB) refers to tuberculosis (TB) occurring within a location in the body other than the lungs (e.g., meninges, lymph nodes, pleura, abdomen, genitourinary tract, skin, joints, and bones) [1]. EPTB is estimated to account for 8–24% (14% of the 6.4 million incident cases on average) of all TB infections worldwide [2]. These numbers vary in accordance with specific risk factors in certain regions worldwide, such as age, sex, concurrent HIV infection, and underlying comorbidities [2, 3]. EPTB commonly occurs in children and HIV-infected individuals [4].

To diagnose EPTB, samples for culturing should be obtained from sites of suspected infection. Diagnosis of pediatric EPTB is challenging because clinical specimens are potentially inaccessible for appropriate sampling and require invasive diagnostic sampling [5]. Furthermore, it takes 8–12 weeks to obtain results through culturing, thus potentially delaying treatment [6]. Because of these diagnostic challenges among children, the incidence of pediatric EPTB is probably underestimated [7].

The Xpert® MTB/RIF assay (Xpert; Cepheid, Sunnyvale, CA, USA) is a cartridge-based nucleic acid amplification assay for rapid TB diagnosis and rapid antibiotic sensitivity analysis. Xpert is thus far the only rapid assay for TB diagnosis currently recommended by World Health Organization (WHO) [2]. Since 2013, Xpert has also been recommended for the diagnosis of TB meningitis and TB lymphadenitis in children [8]. Several systematic reviews are available regarding the diagnostic accuracy of Xpert for EPTB in both pediatric and adult populations; however, none of them reported distinct data for children [5, 9-11].

Therefore, data regarding the accuracy of Xpert exclusively among children are unavailable. We conducted a systematic review and meta-analysis to assess the diagnostic accuracy of Xpert for detecting EPTB among children.

Methods

Data sources and search strategies

We searched MEDLINE, EMBASE, and the Cochrane Infectious Diseases Group Specialized Register. Our last search was carried out on July 16, 2019. Furthermore, we manually reviewed the bibliography of the included articles. The primary search terms were “Xpert,” “GeneXpert,” “Cepheid,” “MTB/RIF,” and “Tuberculosis.” The search methodology applied for each database is shown in Additional File 1. The bibliography was screened for full-length research articles in all languages. Moreover, we conducted a full-text review to select articles exclusively on pediatric EPTB.

Eligibility criteria

The following were the inclusion criteria: (1) studies using Xpert as a diagnostic tool for detecting EPTB in comparison with a reference standard in each study, with all non-respiratory samples (i.e., lymph node aspirate or tissue, CSF, pleural fluid, etc.); (2) studies evaluating the diagnostic performance of Xpert; (3) studies providing pediatric (0–18 years) data. Studies were included regardless of HIV infection.

We excluded reviews, letters, editorials, expert opinions, animal experiments, and studies that only presented as an abstract. Studies that did not include separate pediatric data were also excluded. We attempted to include all types of EPTB samples; however, studies reporting the use of gastric lavage samples were excluded because they were intended for the diagnosis of pulmonary TB. Studies including samples from fewer than five patients and studies with no or insufficient data to construct a 2 × 2 contingency table to determine sensitivity and specificity were also excluded. If data were obtained in more than one article from the same author, the article with the most data was selected.

Study selection

Two review authors (YS Seo and JK Ahn) independently assessed titles and abstracts in accordance with the inclusion and exclusion criteria, followed by a full-text review of the selected studies. Discrepancies regarding the inclusion of articles between the two authors were resolved by the third author (DS Kim).

Composite reference standard (CRS)

To compare the accuracy of Xpert, mycobacterial culturing or a CRS were used as reference standards herein. The CRS was defined by the authors of each study. Owing to paucibacillary characteristics of extrapulmonary TB, the clinical diagnosis of TB was also included. The CRS included histopathological, smearing, and clinical response analysis to treatment with anti-TB therapy along with culturing.

Quality Assessment

Qualitative assessment was performed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [12]. All eligible studies were evaluated on the basis of four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of the risk of bias, and the first three domains were assessed in terms of concerns regarding applicability.

Statistical analysis

We determined the sensitivity and specificity of Xpert with 95% confidence intervals in comparison with culturing or the CRS. To assess heterogeneity among the studies, the chi-square test was performed. Heterogeneity was defined as a *p*-value of <0.10. In case of heterogeneity, different thresholds were considered to influence sensitivity and specificity. To assess the presence of a threshold effect, Spearman's ρ correlation analysis was performed with $\rho > 0.6$ implying a threshold effect. Sensitivities and specificities of Xpert in each study were determined and subjected to the meta-analysis with a bivariate random-effects model. We plotted the summary receiver operating characteristic (sROC) curve with this model. R-package mada (version 3.5.1.) was used to generate forest plots and an ROC curve.

Results

Studies identified

Figure 1 shows the protocol for the screening of articles. Of the 2225 articles obtained from MEDLINE (n=844), EMBASE (n=1180), and Cochrane (n=201), 670 duplicates were excluded. After screening the titles, 1291 studies were excluded, and after screening the abstracts, 162 studies were excluded. After full-text review of the remaining 102 studies, 95 studies were excluded. Finally, 7 studies with 560 samples were included.

Study characteristics

Table 1 summarizes the characteristics of the included studies. Five studies were conducted in Africa [13-17], 1 study in India [18], and 1 in Italy [19]. One study was a cohort study [19] and the remaining 6 were

prospective studies [13-18]. All articles were written in English. Sample numbers varied in accordance with the studies. In total, 247 lymph nodes, 204 CSF samples, and 109 musculoskeletal samples were reviewed.

Quality assessment

Quality assessment was performed using QUADAS-2, as summarized in Figure 2. In the patient selection domain, one study reported a high risk of bias, wherein patients were selected through convenience [14]. Other studies reported a low risk of bias. Regarding applicability, one study (Bholla, M., 2016) had low concern because patients were assessed in a local hospital and another study (Held, M., 2016) had high concern because only inpatients were evaluated at a tertiary-care center [13, 14]. Other studies reported unclear concern due to lack of enough information regarding the clinical setting [15-19]. Regarding the index test and reference standard, the included studies generally had a low risk of bias and low applicability concerns.

Meta-analysis for diagnostic accuracy of Xpert

The 7 studies were evaluated as described above (Figure 3). Regardless of the sample type, the pooled sensitivity and specificity of all samples were 67% (95% CI 0.51-0.79) and 94% (95% CI 0.87-0.98), respectively. The area under the ROC curve was 0.89 (Figure 4). High heterogeneity was confirmed through chi-square analysis for both sensitivity and specificity. However, it was difficult to assign statistical significance because of heterogeneity among the sample types. Therefore, each sample was divided into subgroups.

Detection of lymph node TB

Five studies used Xpert to analyze lymph node samples obtained through fine-needle aspiration biopsy (FNAB) or lymph node biopsy in comparison with a CRS [14, 16-19]. Pooled sensitivity and specificity of lymph node samples were 75% (95% CI 0.54-0.89) and 90% (95% CI 0.77-0.96), respectively. The area under the ROC curve was 0.90. High heterogeneity was confirmed using the chi-square test for both sensitivity and specificity.

Detection of TB meningitis

Four studies used Xpert to analyze CSF samples in comparison with a CRS [15, 17-19]. Pooled sensitivity and specificity of CSF samples were 40% (95% CI 0.23-0.60) and 96% (95% CI 0.85-0.99), respectively. The

area under the ROC curve was 0.56. High heterogeneity was confirmed through chi-square analysis for specificity.

Discussion

The present study summarizes the overall performance of Xpert in the diagnosis of pediatric EPTB based on currently available literature. Although previous systematic reviews analyzed data on both children and adult populations, none of them reported distinct data for children [5, 11]. This study shows that Xpert has high specificity in pediatric EPTB, although its sensitivity is relatively lower and highly variable among specimen types.

In a recent meta-analysis reporting data primarily about adults, the pooled sensitivity varied among different types of specimens (83.1% in lymph node aspirates, 71.1% in CSF, and 94.6% in bone or joint tissue). However, the pooled specificity was relatively high between sample types (86% in lymph node aspirates, 98% in CSF, and 85.3% in bone or joint tissue) [11]. These data are concurrent with the present results in that Xpert showed high specificity among various specimens in our study. Furthermore, the pooled sensitivity varied among the different types of specimens in this study. Overall, however, the sensitivity was lower among children than among adults, especially for CSF samples (40% vs. 71%) [11]. In the case of musculoskeletal TB, the data were insufficient to carry out a meta-analysis for the diagnostic accuracy of Xpert in our study because only one study exclusively reported pediatric data [13]. However, this study also displayed lower sensitivity in children than in adults [13], probably because the sample volume that can be collected from children is relatively less than that from adults and because of the paucibacillary nature of EPTB in the former [15, 18, 20]. For CSF samples, a high sample volume increased the sensitivity of Xpert [21]. The total number of TB bacilli in the test sample plays an important role in the sensitivity of Xpert [21, 22], implying that the sensitivity of Xpert in liquid samples may be lower than expected.

Since 2013, WHO has recommended Xpert rather than conventional tests for the diagnosis of TB meningitis and TB lymphadenitis in children. Per the 2013 WHO data, the pooled sensitivity and specificity of lymph node TB in children were 86% (95% CI 0.65-0.96) and 81% (95% CI 0.54-0.93), respectively. In the case of TB meningitis, the pooled specificity was 95% (95% CI 0.81-0.99) and the sensitivity could not be determined owing to insufficient data [8]. To our knowledge, this is the first meta-analysis to evaluate the sensitivity of Xpert for TB meningitis only in pediatric populations. Our results suggest that negative Xpert results in children should be interpreted with caution with respect to ruling out pediatric TB meningitis. However, since TB meningitis is potentially lethal in children, the rapidity of Xpert explains why it should be used as an initial diagnostic test for TB meningitis despite its low sensitivity.

Recently, the next-generation Xpert MTB/RIF assay, Xpert MTB/RIF Ultra assay (Cepheid) (ULTRA), has been developed with a limit of detection enhanced by ~8-fold that of the previous Xpert MTB/RIF assay; it includes a larger chamber and additional molecular targets [23]. In 2017, WHO recommended the use of ULTRA as a replacement for Xpert MTB/RIF in all settings [24]. A single study of TB meningitis conducted in Uganda assessed the diagnostic accuracy of Xpert and ULTRA in comparison with a CRS on the basis

of positive CSF culture, Xpert, or ULTRA results. Consequently, the sensitivity of detection of MTB for CSF was 95% for ULTRA (21 out of 22) relative to 45% for Xpert MTB/RIF (10 out of 22) [25]. ULTRA is expected to have higher sensitivity for EPTB. However, as discussed herein, pediatric EPTB samples showed lower sensitivity than adult samples. ULTRA would be helpful for the paucibacillary population, especially in terms of diagnostic sensitivity. However, considering that the sensitivity of the previous version of Xpert is low in children and yielded different values among samples, further studies are required to determine the reliability of the negative results.

The present meta-analysis exhibited high heterogeneity in both TB lymphadenitis and meningitis. Although the population was limited to pediatric age and samples were divided into subgroups, differences in processing methods for samples and a small sample size may have resulted in high heterogeneity.

Conclusions

In diagnosing pediatric EPTB, Xpert displayed high specificity regardless of specimen type, but modest sensitivity, which varied among specimen types. In particular, in CSF samples, Xpert displayed the lowest sensitivity in comparison with the CRS. Although positive Xpert results can be considered to indicate presumptive EPTB in children, EPTB cannot be ruled out on the basis of negative test results. Future clinical trials are required to expand the evidence base for Xpert for diagnosis of pediatric EPTB with different forms of extrapulmonary specimens in various clinical settings.

Abbreviations

CI: Confidence interval, CRS: composite reference standard, CSF: Cerebrospinal fluid,

EPTB: Extrapulmonary tuberculosis, FNAB: Fine needle aspiration biopsy, LN: Lymph node,

TB: Tuberculosis, ULTRA: Xpert MTB/RIF Ultra assay

ROC: Receiver operating characteristic.

Declarations

Ethics approval and consent to participate

No institutional review board approval or ethics statement was required as the present meta-analysis followed a retrospective design.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are appropriately cited.

Competing interests

The authors declare no conflicts of interests.

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Authors' contributions

JGA devised the review, the main conceptual ideas, and proof outline. YSS primarily collected the data, performed preliminary data analysis, and wrote the manuscript. JMK and DSK participated in the study design and data evaluation. JGA supervised the design and execution of the study, interpreted the final data, and contributed to writing of the manuscript. All authors approved the manuscript for publication.

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Not applicable.

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Tables

Table 1. Characteristics of the included studies

Study	First author	Year	Country	Setting	Age	Study Design	HIV%	Culture reference standard	Composite reference Standard (CRS)	Total samples (n)	Specimen type
1	Bholla, M.	2016	Tanzania	Primary care Center	8 weeks~ 16 years	Prospective	20	MGIT	Cytology and/or Culture	75	Lymph node
2	Coetzee, L.	2014	South Africa	Tertiary care center	< 13 years	Prospective	8.3	MGIT	Cytology and/or Culture	72	Lymph node
3	Das, A.	2019	India	Tertiary care center	4 months~ 14 years	Prospective	1.75	MGIT/LJ	Culture	57	Lymph node (n=6), CSF (n=51),
4	Held, M.	2016	South Africa	Tertiary care center	< 13 years	Prospective	10	MGIT	Culture or histology	109	Bone and joint tissue biopsy
5	Solomons, R.S.	2015	South Africa	Tertiary care center	3 months~ 13 years	Prospective	11	MGIT	Clinical TBM reference standard	101	CSF
6	Tortoli, E.	2012	Italy	Tertiary care center	0–18 years	Retrospective	10	MGIT/LJ	Histopathology /Improvement on ATT	132	Lymph node (n = 89), CSF (n = 43),
7	Vadwai	2011	South Africa	Tertiary care center	< 13 years	Prospective	3	MGIT	Histopathology /Improvement on ATT	14	Lymph node (n=5), CSF (n=9)

MGIT, mycobacterial growth indicator tube; LJ, Löwenstein-Jensen culture; CSF, cerebrospinal fluid

Figures

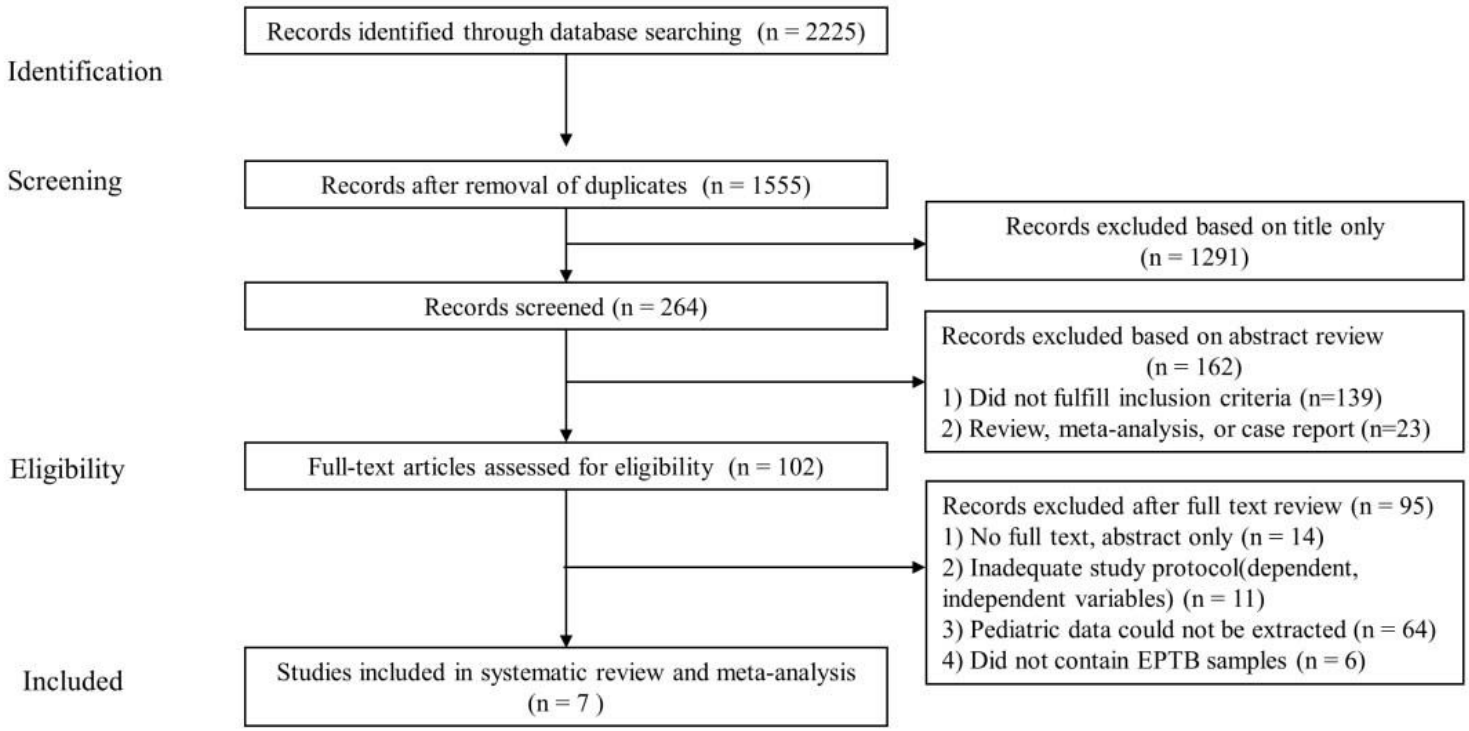

Figure 1

Flow diagram showing the protocol for study selection. EPTB, extrapulmonary tuberculosis.

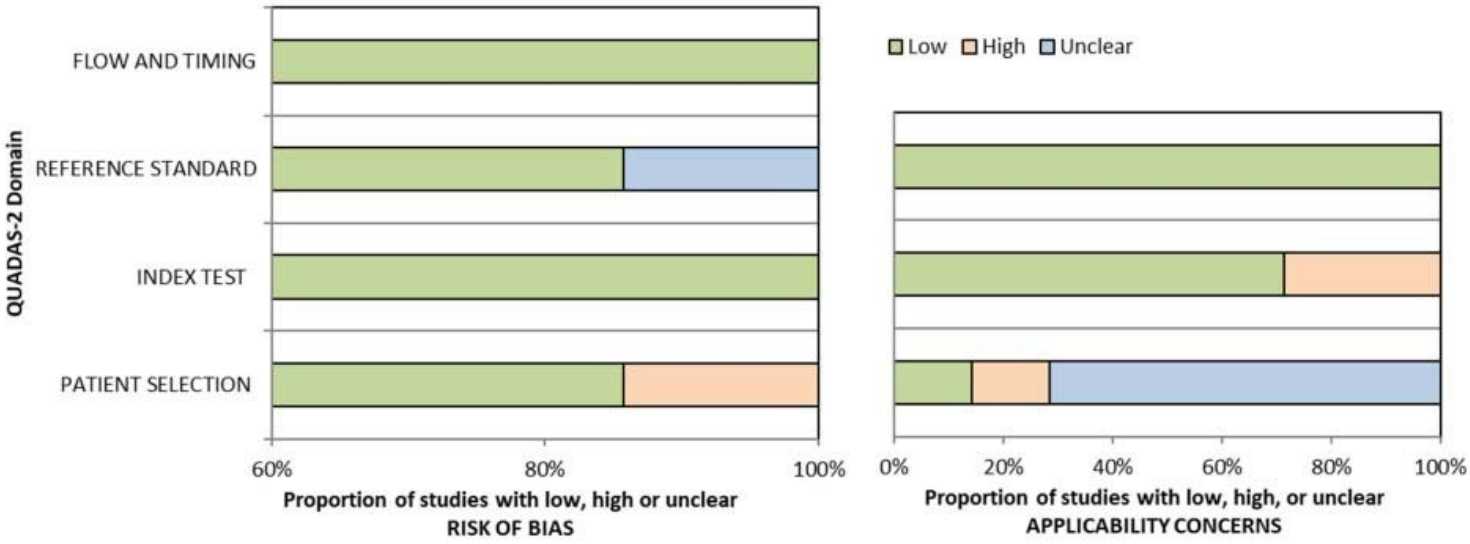

Figure 2

Quality assessment based on the Quality Assessment of the Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines. Graphical representation of the risk of bias and applicability concerns.

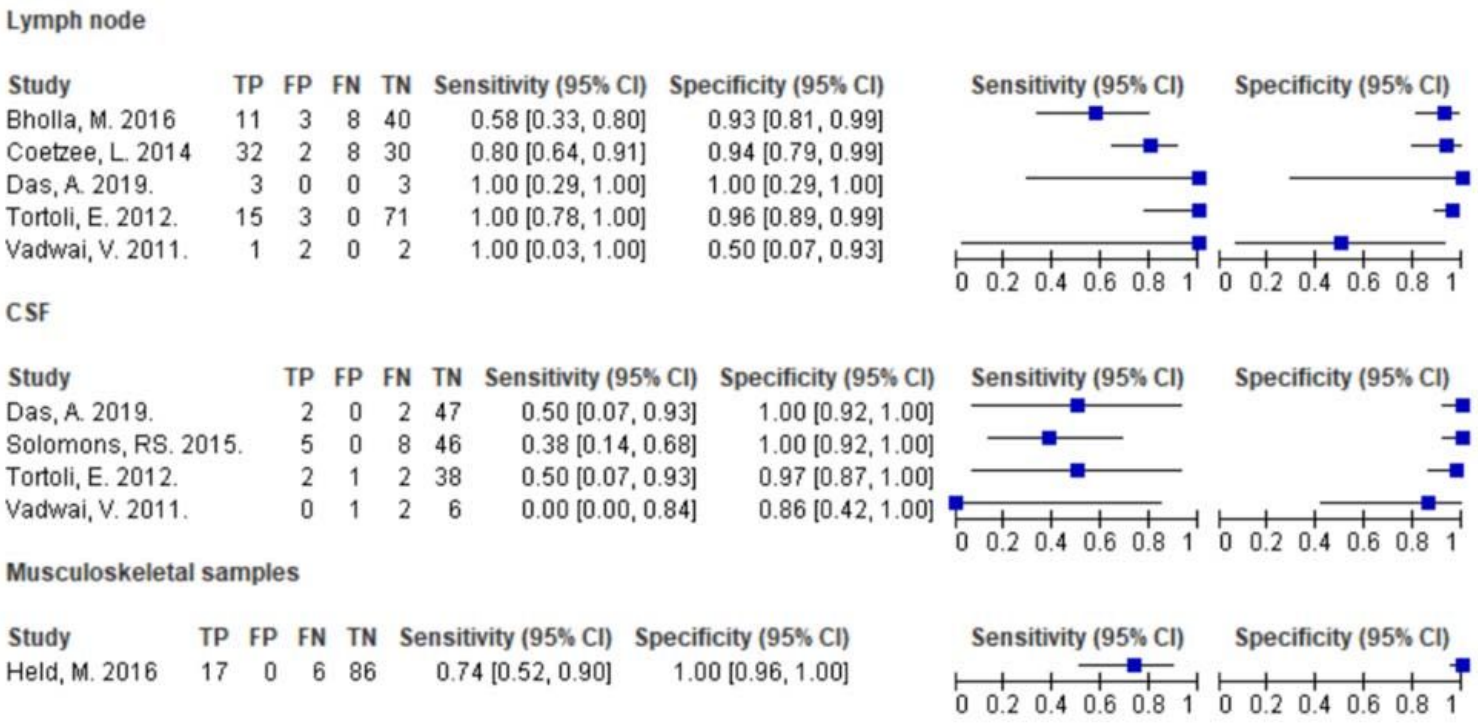

Figure 3

Forest plot of the sensitivity and specificity of Xpert in diagnosing extrapulmonary tuberculosis in comparison with a composite reference standard in accordance with the study and specimen type. TP, true positive; FP, false positive; FN, false negative; TN, true negative.

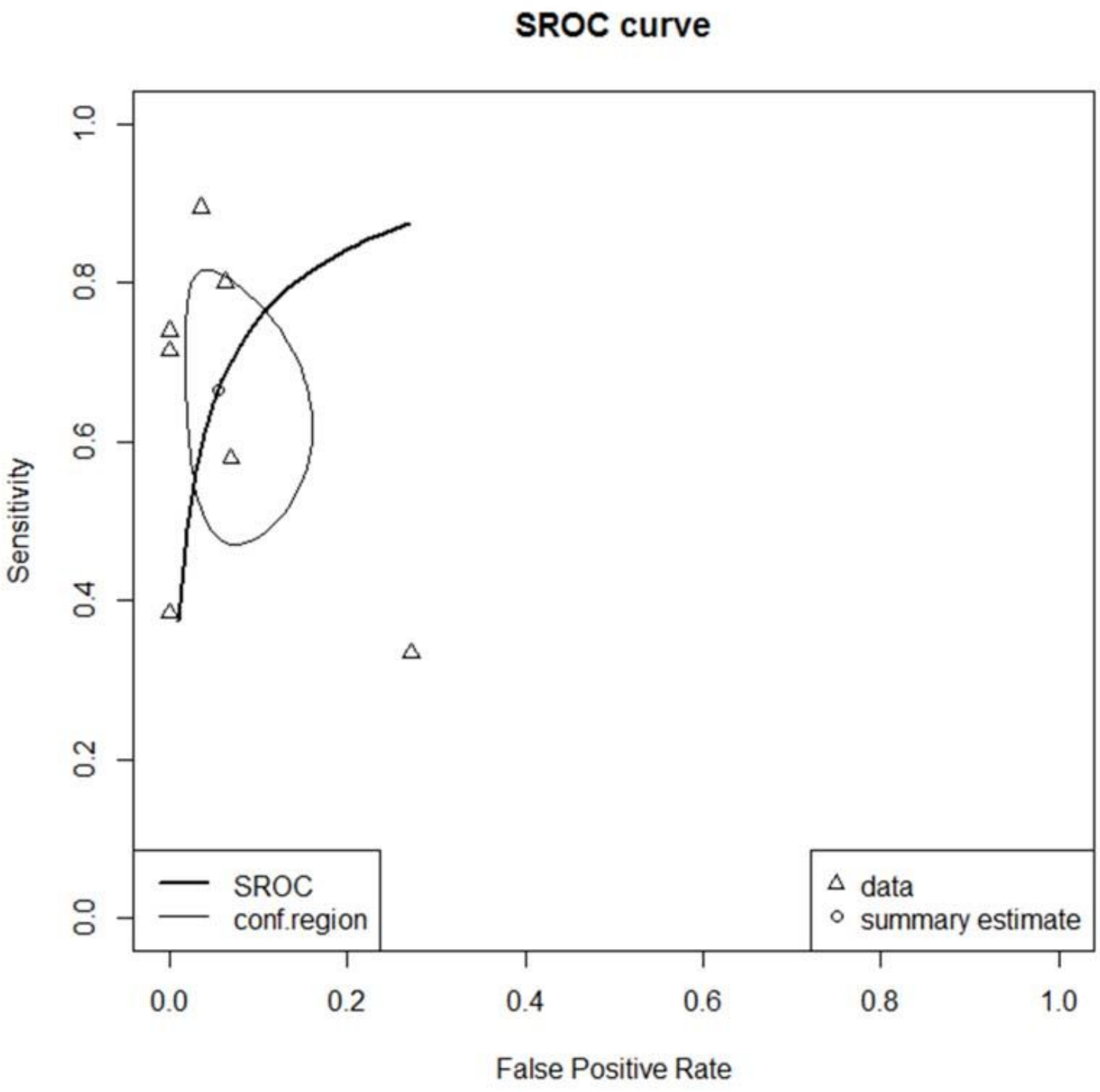

Figure 4

Hierarchical summary receiver operating characteristic (HSROC) curve of the diagnostic accuracy of Xpert® MTB/RIF assay (Xpert) for extrapulmonary tuberculosis (EPTB). Summary points of the sensitivity and specificity, the HSROC curve, and 95% confidence intervals are provided herein. The area under the curve of the HSROC for Xpert was 0.89.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.xlsx