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Systematic Review

# Diagnostic accuracy of Xpert MTB/RIF for tuberculous meningitis: systematic review and meta-analysis

**Adrian V. Hernandez[1,2], Laryssa de Laurentis[3], Isadora Souza[3], Marcelo Pessanha[3], Priyaleela Thota[4], Yuani M. Roman[1], Joshuan Barboza-Meca[2], David R. Boulware[5] and Jose E. Vidal[6,7]**

1 *University of Connecticut/Hartford Hospital Evidence-based Practice Center, Hartford, CT, USA*
2 *Vicerrectorado de Investigación, Universidad San Ignacio de Loyola (USIL), Lima, Peru*
3 *Department of Infectious Diseases, Instituto de Infectologia Emílio Ribas, São Paulo, Brazil*
4 *Hemex Health Inc., Portland, OR, USA*
5 *Department of Medcine, University of Minnesota, Minneapolis, MN, USA*
6 *Department of Neurology, Instituto de Infectologia Emílio Ribas, São Paulo, Brazil*
7 *Department of Infectious Diseases, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*

**Abstract**

OBJECTIVE This systematic review evaluated the diagnostic accuracy of Xpert MTB/RIF to detect tuberculous meningitis (TBM).

METHODS PubMed and five other databases were systematically searched through March 2019. All studies evaluating diagnostic accuracy of Xpert MTB/RIF on cerebrospinal fluid (CSF) samples were included. Reference standards were definitive or definite plus probable TBM. The quality of studies was assessed by the QUADAS-2 tool. We performed bivariate random-effects meta-analysis and calculated summary diagnostic statistics.

RESULTS We identified 30 studies ($n$ = 3972 participants), including 5 cohort studies and 25 cross-sectional studies. Reference standards were definite TB ($n$ = 28 studies) or definite plus probable TBM ($n$ = 6 studies). The pooled Xpert MTB/RIF sensitivity was 85% (95% CI, 70–93%), and specificity was 98% (95% CI, 97–99%) with a negative likelihood ratio of 0.15 (95% CI, 0.04–0.27) for definite TBM. For probable TBM cases, pooled sensitivity was 81% (95% CI, 66–90%), and specificity was 99% (95% CI, 97–99%). For both reference standard types, meta-analyses showed a C-statistic area under the curve of 0.98. The QUADAS-2 tool revealed low risk of bias as well as low concerns regarding applicability. Methodological heterogeneity was high among studies.

CONCLUSIONS Xpert MTB/RIF showed high accuracy for TBM diagnosis, but a negative Xpert MTB/RIF test does not rule out TBM. Repeat Xpert testing may be necessary. In clinical practice, Xpert MTB/RIF adds speed and sensitivity when compared to classic TBM diagnostic methods or previous commercial nucleic acid amplification techniques. More studies and better strategies for rapidly confirming a diagnosis of TBM in children are urgently needed.

**keywords** Tuberculous meningitis, tuberculosis, Xpert MTB/RIF, diagnosis, systematic review

**Sustainable Development Goals (SDGs):** 3.3.2, 3.b

## Introduction

Tuberculosis (TB) is a common opportunistic infection and is a leading cause of hospitalisation and in-hospital death among people living with HIV/AIDS (PLWHA) worldwide [1], particularly in developing countries [2–4].

Up to 25% of tuberculosis cases in PLWHA may present with extrapulmonary tuberculosis [5, 6] and tuberculous meningitis (TBM) represents approximately 5% of extrapulmonary tuberculosis [6]. TBM is the most severe presentation of tuberculosis, and it is the second most common cause of HIV-associated opportunistic meningitis [7, 8]. In spite of adequate chemotherapy, TBM cause death or severe neurological defects in more than half of those affected [9, 10].

Although some clinical and basic cerebrospinal fluid (CSF) features appear useful in the differential diagnosis of TBM and cryptococcal meningitis in PLWHA, an

accurate discriminatory algorithm is not available with this information [11, 12]. The classical 'gold standard' for TBM diagnosis is the demonstration of *M. tuberculosis* bacilli in the CSF. However, smear microscopy is rapid but only ~10–20% sensitive. Culture has ~50% sensitivity but is slow (at least 10 days in liquid media and up to 8 weeks on solid media), and culture ideally requires a biosafety level 3 laboratory [13, 14]. Commercial nucleic acid amplification tests for TBM show sensitivities of 56–64% and specificity of 98% [10, 15, 16] and 'in house' nucleic acid amplification tests for TBM show high heterogeneity of protocols and performance [10, 12].

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is a cartridge-based fully automated, real-time polymerase chain reaction (PCR) system which detects *M. tuberculosis* DNA in ~2 h [17]. In 2013, WHO endorsed the Xpert MTB/RIF assay as the preferred initial test to investigate TBM [18, 19]. Nowadays, Xpert MTB/RIF assay is widespread, including U.S. FDA-approval and European CE marking, and has the capacity to be used both in central laboratories or near bedside laboratories [20]. Prior to this assay, molecular diagnosis of TBM was limited only to specialised laboratories.

We performed a systematic review and meta-analysis in order to estimate the diagnostic performance of Xpert in TBM.

## Methods

This review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement guidelines [21].

### Data sources and searches

We performed a systematic search for publications using PubMed-OVID, EMBASE, Scopus, Web of Science, Cochrane Library, Google Scholar until 1 March 2019. Duplicates were removed, and abstracts reviewed for selection. The words were as follows: 'Xpert' ', 'Xpert MTB/ RIF', 'GeneXpert', 'GeneXpert MTB/ RIF', 'Cepheid', 'tuberculous meningitis', 'tuberculosis meningitis', 'central nervous system tuberculosis', and 'Mycobacterium tuberculosis'. The search strategy for PubMed is available in the Supplement.

### Selection of studies

Inclusion criteria were as follows: (i) studies reporting diagnostic accuracy of the Xpert MTB/RIF test for TBM; (ii) prospective cohorts, retrospective cohorts or cross-sectional study designs; (iii) studies including adults or children (<18 years old); (iv) studies using one or two prespecified diagnostic reference standards: definite TBM by microbiologic confirmation, or definite plus probable TBM by a case definition; (v) studies with more than 5 clinical samples; and (vi) studies with complete data: true positives, true negatives, false positives and false negatives. All languages were included. We excluded conference abstracts.

Based on inclusion and exclusion criteria, selection of studies was performed independently by four authors (JEV, LL, IS and MP). Full texts of selected studies were also evaluated to reach selection decisions. Disagreements were resolved with discussion with author (AVH).

### TBM diagnostic reference standards

In this systematic review, we used the Marais uniform case definition criteria to classify the TBM categories into: (i) 'definite TBM' cases with microbiologic confirmation in the CSF by culture, microscopy, or commercial DNA nucleic acid amplification test; and (ii) 'probable TBM' cases with a Marais score of 7–12, indicating a higher risk of a TBM diagnosis [22]. If a study did not use explicitly the Marais criteria to classify the 'definite TBM' but the criteria of microbiologic confirmation was compatible, we considered the author criteria as Marais criteria. If a study did not use the category of 'probable TBM' of Marais criteria, the authors' specific criteria were used.

### Extraction of data

A pre-defined Excel extraction form included study first author, year of publication, country(ies) where study was performed, sample size, study design, median age, percentage of women, percentage of HIV-infected participants, median CSF volume, use of centrifuged CSF, type (s) and definitions of TBM diagnostic reference standard (s), true positives, true negatives, false positives and false negatives. Four authors independently performed data extraction, and disagreements were resolved by discussion with a senior author. If there were several studies of the same population, we used the most recent and largest, published population.

### QUADAS-2 risk of bias assessment

We used the QUADAS-2 tool for the evaluation of the risk of bias in diagnostic studies [23]. This tool comprises four domains: patient selection, index test, reference

standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed in terms of concerns regarding applicability.

### Data analyses

Analyses were stratified by reference standard type. For meta-analyses, we used the random-effects bivariate model of Chu and Cole, which was fitted as a generalised linear mixed effect model using the *glmer* function from the package lme4 of R [24]. Models were run at the publicly available webpage metaDTA (https://crsu.shinyapps.io/dta_ma/). The bivariate model takes into account the correlation between sensitivity and specificity. We calculated sensitivity, specificity, positive likelihood ratio (+LR) and negative LR (−LR), with their 95% confidence intervals (95% CI) as summary measures. We presented a receiver operating characteristic (ROC) curve summary area under the curve (i.e. C-statistic). As we anticipated methodologic heterogeneity across studies, we pre-specified subgroup analyses by country where study was conducted (high-income vs low- or middle-income country), CSF sample centrifugation (centrifuged vs non-centrifuged), CSF volume and HIV-infection status.

## Results

### Eligible studies

Of the 1656 unique articles retrieved and screened by study title, 845 potentially relevant articles were selected based on relevance to the study topic. After screening the abstracts, 118 articles were found to fulfil the inclusion criteria and were selected for full-text review (Figure 1). Thirty articles ($n$ = 3972) assessing the performance of Xpert MTB/RIF for TBM were included in our systematic review and meta-analysis [14, 25–53].

### Study characteristics

Table 1 summarises the main characteristics of the included studies. There were 5 cohort studies ($n$ = 1442) and 25 cross-sectional studies ($n$ = 2530). Twenty-eight studies used definite, microbiologically proven cases as reference standard, and 6 studies used definite plus probable TBM cases. In three studies, the authors used their own criteria to define probable TBM. Seven studies were performed in high-income countries, and 23 studies were performed in low- or middle-income countries.

The range of sample sizes was 6 to 740. Only 5 studies included children and/or adolescents. The median age ranged from 30 to 50 in 9 studies with available information. Women comprised 27% to 53% of participants in studies with available information. In 15 studies CSF was centrifuged, and in 11 studies CSF was not centrifuged. The CSF volume tested ranged from 0.2 to 2 mL with one study reporting as ≥ 0.5 mL. HIV-infected individuals comprised 0% to 100% of participants in 12 studies with available information.

### Risk of bias assessment

Overall four studies had high risk of bias [32, 37, 43, 53] (Table 2). There was low risk of bias in most of studies about patient selection and flow and timing. Two studies showed high risk in patient selection [37, 53]. Two studies showed high risk in flow and timing [32, 43] being collected post-mortem or at TB-referral hospital. There was unclear risk of bias for all studies about index and reference tests, due to the problematic, imperfect reference standard of TBM. Most studies had applicability concerns about the reference standard, with the exception of 9 studies which utilised explicitly the Marais uniform case TBM definition [14, 26, 29, 31, 32, 34, 39, 48, 52].

### Meta-analysis of diagnostic accuracy of Xpert

The overall pooled estimates of Xpert MTB/RIF tests for definite cases were as follows: sensitivity of 85% (95% CI, 70–93%), specificity of 98% (95% CI, 97–99%), +LR of 44.8 (95% CI, 17.2–72.4) and -LR of 0.15 (95% CI, 0.04–0.27) (Figure 2a). For definite plus probable TBM cases, the pooled estimates were as follows: sensitivity of 81% (95% CI, 66–90%), specificity of 99% (95% CI, 97–99%), +LR of 53 (95% CI, 14.2–90.7) and -LR of 0.20 (95% CI, 0.07–0.32), respectively (Figure 2b). For both reference standard types, meta-analyses showed areas under the summary ROC area under the curve above 98%.

### Subgroup analyses

Subgroup analyses by country where study was conducted (high-income versus low or middle country) and by with/without centrifugation of CSF sample provided similar results as the main analyses for both TBM reference standards. The sensitivity of Xpert MTB/RIF for definite TBM did not differ between high-income countries (sensitivity of 97%; 95% CI, 42–100%) versus low- or middle-income countries (sensitivity of 80%; 95% CI, 63–91%). Specificitity also did not differ. Xpert MTB/RIF tests with centrifugation showed both similar sensitivity when compared with tests performed without centrifugation [84% (95% CI, 65–94%) versus 86% (95%

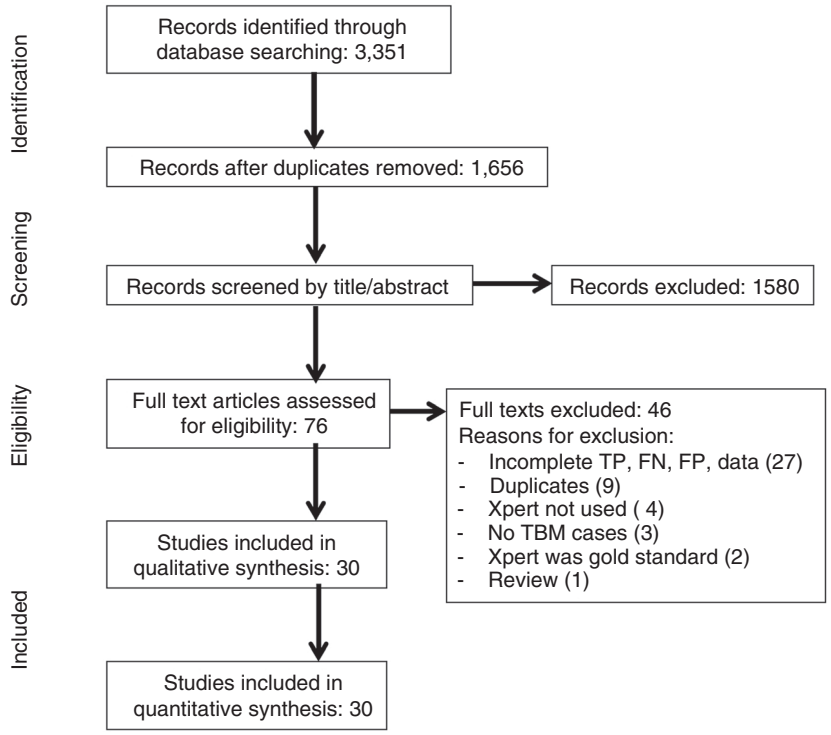



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies flow chart for the selected studies.

CI, 58–96%), respectively, although differing volumes being centrifuged were utilised across studies (see Figures S1–S8). Centrifuging a CSF volume < 2 mL would provide no effect as there is no net increase in input volume for the Xpert cartridge. There was limited information about CSF volume, paediatric population and HIV status, and no subgroup analyses were possible.

## Discussion

In this study, Xpert MTB/RIF showed high accuracy for definite TBM or for definite plus probable TBM with an estimated pooled sensitivity of 85% (95% CI 70–93%). For both reference standard types, meta-analyses showed very high areas under the summary ROC and the QUADAS-2 tool revealed low risk of bias for most of the studies.

Definite diagnosis of TBM is difficult particularly in low- and middle-income countries because microscopy has low sensitivity, culture takes long time, and commercial nucleic acid amplification techniques have moderate sensitivity and are expensive. In clinical practice of most low and middle-income countries, the diagnosis of TBM is usually based on a combination of clinical, laboratory and radiological findings but scaling up Xpert implementation adds the opportunity of timely diagnosis.

The diagnostic accuracy of Xpert MTB/RIF for TBM has been evaluated in prior systematic reviews and meta-analyses [54–58]. When Xpert MTB/RIF was evaluated in definite cases, the sensitivity ranged from 61 to 85% and specificity from 97% to 100% [54–58]. When Xpert MTB/RIF was evaluated versus a composite reference standard, the sensitivity ranged from 62.8% to 66% and specificity from 89% to 98.8% [54, 57]. In most studies, CSF cultures were the gold standard; however, culture has only moderate sensitivity (30–60%) [59–61]. Xpert MTB/RIF is a ruled-in diagnostic test, but a negative result does not provide adequate confidence that TBM is not present [62]. In contrast to conventional microscopy culture, Xpert MTB/RIF provides a timely diagnosis and is readily available in most settings where tuberculosis is endemic. For these reasons, Xpert MTB/RIF should be used as the initial diagnostic test for CSF specimens from patients presumed to have TBM [18]. However, culture is an imperfect gold standard of TBM, and the reported < 100% specificity of Xpert MTB/RIF versus a

**Table 1** Overview of characteristics of included studies

| Authors, year Ref | Study design | Country | *N* | TBM definition per Marais' criteria (*n*) | Age in years | Women | HIV | CSF volume mL | CSF centrifuged? |
|---|---|---|---|---|---|---|---|---|---|
| Teo (2011) | Cross-sectional | Singapore | 7 | Definite TBM (2) | NA | NA | NA | 0.5 | Yes |
| Vadwai (2011) | Cross-sectional | India | 23 | Definite TBM (3) | NA | NA | NA | 1 | Yes |
| Moure (2012) | Cohort | Spain | 14 | Definite TBM (2) | NA | NA | NA | 1 | Not |
| Tortoli (2012) | Cross-sectional | Italy | 131 | Definite TBM (11) | All | NA | NA | ≥ 0.5 | Yes |
| Nhu (2013) | Cross-sectional | Vietnam | 379 | Definite TBM (29) | >18 | NA | 21% | 0.2 | Yes |
| Zmak (2013) | Cross-sectional | Croatia | 46 | Definite TBM (1) | NA | NA | NA | 0.5 | Yes |
| Patel (2014) | Cross-sectional | South Africa | 148 | Definite TBM (36) | 33 (±8)‖ | 52% | 90% | 1 | Not |
| Cox (2015) (Arm 1) | Cross-sectional | Uganda | 14 | Definite TBM (8) | >18 | NA | NA | 1 | Not |
| Cox (2015) (Arm 2) | Cross-sectional | Uganda | 14 | Definite TBM + Probable TBM§ (14 in total) | >18 | NA | NA | 1 | Not |
| Kim (2015) | Cross-sectional | South Korea | 254 | Definite TBM + Probable TBM† (4 in total) | 50 (34–63)§ | 44% | 2% | NA | Yes |
| Solomons (2015) (Arm 1) | Cohort | South Africa | 101 | Definite TBM (13) | 3 (2–5) | 53% | 11% | 1 | Not |
| Solomons (2015) (Arm 2) | Cohort | South Africa | 101 | Definite TBM + Probable TBM (23 in total) | 3 (2–5) | 53% | 11% | 1 | Not |
| Mazzola (2016) | Cross-sectional | Italy | 160 | Definite TBM (7) | NA | NA | NA | 0.5 | Not |
| Nataraj (2016) | Cross-sectional | India | 160 | Definite TBM (36) | NA | NA | NA | 1 | NA |
| Peñata (2016) | Cross-sectional | Colombia | 155 | Definite TBM (6) | NA | NA | NA | 1 | Yes |
| Pink (2016) | Cohort | United Kingdom | 740 | Definite TBM (37) | 46 (0–93)¶ | 41% | NA | 1.5 | Yes |
| Wang (2016) (Arm 1) | Cohort | China | 350 | Definite TBM (13) | 32 (1–87)¶ | 41% | NA | 1 | Yes |
| Wang (2016) (Arm 2) | Cohort | China | 350 | Definite TBM + Probable TBM (104 in total) | 32 (1–87)¶ | 41% | NA | 1 | Yes |
| Yuan (2016) | Cross-sectional | China | 17 | Definite TBM + Probable TBM‡ (16 in total) | All | NA | 0% | NA | NA |
| García (2017) | Cross-sectional | Chile | 6 | Definite TBM (2) | NA | NA | NA | 1 | Not |
| Rufai (2017) | Cross-sectional | India | 267 | Definite TBM (49) | 36 (± 15) | 41% | NA | 1 | Not |
| Jing (2017) | Cross-sectional | China | 81 | Definite TBM (12) | NA | NA | NA | 1 | Not |
| Li (2017) | Cross-sectional | China | 74 | Definite TBM (6) | 49 (±10)** | 39% | NA | 2 | Yes |
| Pandey (2017) | Cross-sectional | Australia | 10 | Definite TBM (2) | NA | NA | NA | 0.5 | Not |
| Philip (2017) | Cross-sectional | Malaysia | 55 | Definite TBM (1) | NA | NA | NA | 1 | Yes |
| Ullah (2017) | Cross-sectional | Pakistan | 30 | Definite TBM (6) | NA | NA | NA | 2 | NA |
| Azevedo (2018) | Cross-sectional | Brazil | 101 | Definite TBM (6) | >16 | NA | 100% | 1 – 2 | Not |
| Bahr (2018) (Arm 1) | Cross-sectional | Uganda | 129 | Definite TBM (14) | 32 (30–34)§ | 41% | 100% | 1 | Yes |
| Bahr (2018) (Arm 2) | Cross-sectional | Uganda | 129 | Definite TBM + Probable TBM (23 in total) | 32 (30–34)§ | 41% | 100% | 1 | Yes |

**Table 1** (*Continued*)

| Authors, year Ref | Study design | Country | *N* | TBM definition per Marais' criteria (*n*) | Age in years | Women | HIV | CSF volume mL | CSF centrifuged? |
|---|---|---|---|---|---|---|---|---|---|
| Chaidir (2018) | Cohort | Indonesia | 237 | Definite TBM (88) | 30 (24–38)§ | 45% | 17% | 0.2 | Yes |
| Das (2018) | Cross-sectional | India | 51 | Definite TBM (4) | <15 | NA | 0% | 1 | Yes |
| Metaferia (2018) | Cross-sectional | Ethiopia | 184 | Definite TBM (10) | >18 | 48% | 19% | 2 | Not |
| Metcalf (2018) | Cross-sectional | USA | 37 | Definite TBM (8) | >18 | 27% | 62% | 2 | Yes |
| Mbuh (2019) | Cross-sectional | Cameroon | 11 | Definite TBM (1) | 40 (±19)‖ | 48% | 34% | NA | NA |

Definition of probable tuberculous meningitis (TBM):
*Tuberculosis elsewhere + 2 of the following: clinical, macroscopic or microscopic changes not typical for but consistent with tuberculous meningitis.
†Culture-negative but showing clinical symptoms, radiographic features and/or histology suggestive of tuberculosis, e.g., presence of caseating granuloma in tissue or lymphocyte-dominant pleural effusion with high adenosine deaminase.
‡This study use a composite reference standard diagnosis of extrapulmonary tuberculosis that included the following criteria: (1) all culture-confirmed cases (in this group, microscopy may or may not be positive); (2) microscopy-positive cases with imaging suggestive of TB; (3) pathology confirmed for TB; and (4) all the above tests negative, with only clinical symptoms, imaging findings, and a response to empirical anti-tuberculosis treatment.
§Median (IQR).
‖Mean (±SD).
¶Median (range).
**Median (±SD) as reported.

composite reference standard reflects the current limitations of the reference standard, when excluding the first line Xpert MTB/RIF.

In the present study, we performed two subgroup analyses. First, we compared the accuracy of Xpert MTB/RIF in developed versus developing countries. This analysis has never been performed in prior studies and showed similar results. Second, we evaluated the accuracy of Xpert MTB/RIF with or without centrifugation of samples and the results were similar. In contrast, two systematic review and meta-analysis reported better Se when centrifugation was performed (74.8–84.2%) versus when centrifugation was not performed (51.3–66.2%). In addition, Sp was lightly better when centrifugation was performed (98–98.3%) versus when centrifugation was not performed (94.6–97.7%) [54, 58]. These results confirm the recommendation of experts of use centrifugation of CSF samples in order to improve the accuracy of Xpert MTB/RIF [17, 61, 63].

In our study, the evaluation of CSF volume and HIV status was not possible due to the lack of information. Only one systematic review and meta-analysis evaluated this variable [58] but only individual information was cited, indicating that five studies reported the following relation between CSF volume and Se: 7 mL, 85% [29]; 6 mL, 58% [61]; 6 mL, 60% [58]; 3 mL, 81% [31]; and 2 mL, 52% [42]. Specificities in the five studies were ≥ 93% [58]. Thus, higher volume of CSF seems to improve the diagnosis performance of Xpert MTB/RIF [17, 64] but more studies are necessary to define the ideal volume. In the meanwhile, emphasis on the large CSF volumes (>5 mL) needed for Xpert testing is suggested by experts [63]. About the status of HIV infection, only one study mentioned that sensitivity ranged from 58 to 81% in HIV-positive people compared with 33–100% in studies involving HIV-negative people [58].

Pai *et al.,* before of the availability of Xpert MTB/RIF, reported a systematic review and meta-analysis to establish the accuracy of commercial nucleic acid amplification tests for TBM [15]. The analysis of 14 studies showed sensitivity of 56% (95% CI, 46–66%), specificity of 98% (95% CI, 97–99%), LR + 35.1 (95% CI, 19.0–64.6) and LR− 0.44 (95% CI, 0.33–0.60). Recently, Pormohammad *et al.,* reported a systematic review and meta-analysis of 28 datasets to evaluate the accuracy of commercial nucleic acid amplification tests (including Xpert MTB/RIF) for TBM [57]. Se, Sp, LR+ and LR− of commercial tests against culture were 67% (95% CI 58–75%), 99% (95% CI 98–99%), 46.1 (95% CI 28.3–75.0) and 0.33 (95% CI 0.25–0.43), respectively. Thus, the chronological comparison of these two studies suggests that the availability of Xpert MTB/RIF

**Table 2** Risk of bias assessment of included studies

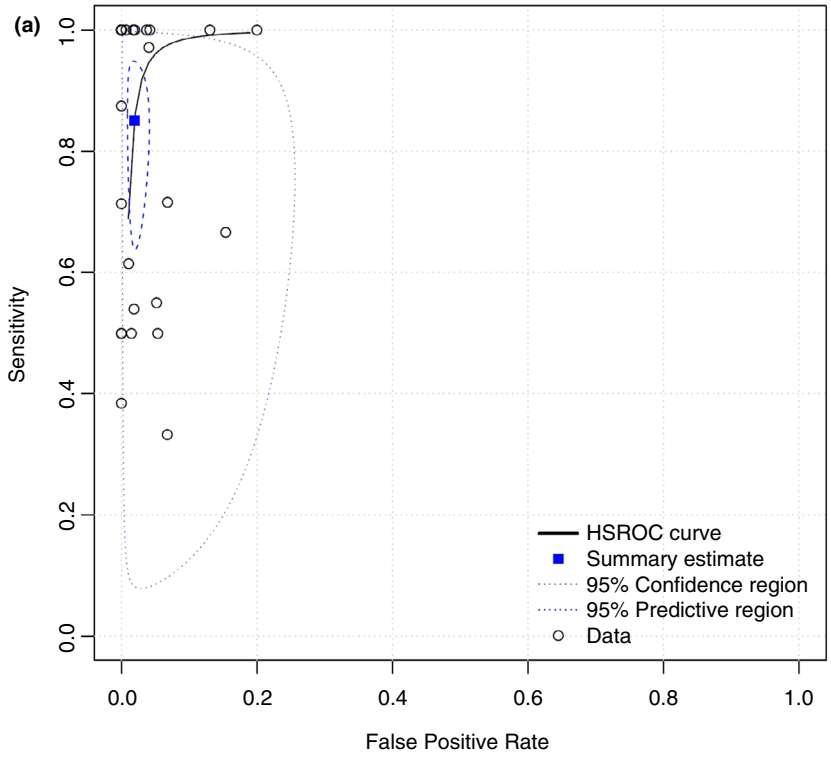
| | Risk of bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| Author, Year | Patient selection | Index tet | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Azevedo, 2018 | ? | ? | ? | ? | ☺ | ☺ | ☺ |
| Bahr, 2018 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Chaidir, 2018 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Cox, 2015 | ☺ | ? | ? | ☹ | ☺ | ☺ | ☺ |
| Das, 2018 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Garcia, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Jing, 2017 | ☺ | ? | ? | ☹ | ☺ | ☺ | ? |
| Kim, 2015 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Li, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Mazzola, 2016 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Mbuh, 2019 | ☹ | ? | ? | ☺ | ☺ | ☺ | ? |
| Metaferia, 2018 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Metcalf, 2018 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Moure, 2012 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Nataraj, 2016 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Nhu, 2013 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Pandey, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Patel, 2014 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Peñata, 2016 | ☹ | ? | ? | ☺ | ☺ | ☺ | ? |
| Philip, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Pink, 2016 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Rufai, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Solomons, 2015 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Teo, 2011 | ? | ? | ? | ☺ | ☺ | ☺ | ? |
| Tortoli, 2012 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Ullah, 2017 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Vadwai, 2011 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Wang, 2016 | ☺ | ? | ? | ☺ | ☺ | ☺ | ☺ |
| Yuan, 2016 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |
| Zmak, 2013 | ☺ | ? | ? | ☺ | ☺ | ☺ | ? |

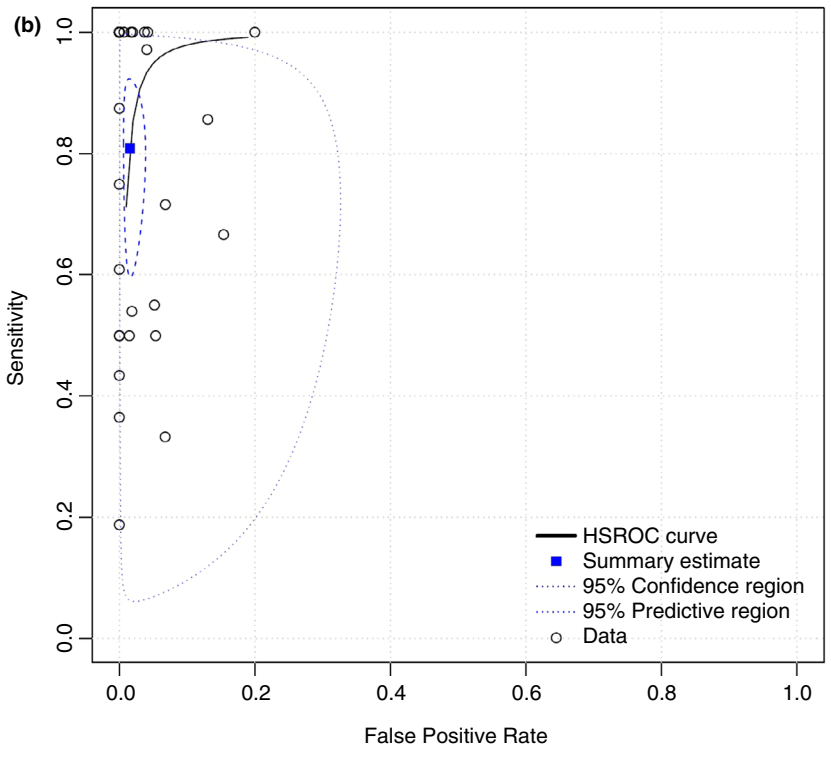
☺ Low risk of bias;☹ High risk of bias; ? Unclear risk of bias.

improved the accuracy of molecular diagnosis of tuberculous meningitis.

Our study has several limitations. First, in diagnostic accuracy studies, an imperfect reference standard may lead to a misclassification of samples. This situation can be the case of the present study where the diagnosis of TBM is complex and limited. Second, in this study, we evaluated only Xpert MTB/RIF but not the next generation Xpert MTB/RIF Ultra (Xpert Ultra) tests, which demonstrated greater sensitivity when compared with culture or Xpert MTB/RIF for TBM diagnosis [14, 65, 66]. WHO now recommends the use of Xpert Ultra as the initial diagnostic test for suspected TBM [67, 68]. Despite Xpert Ultra seems to have some improvement on Xpert, its negative predictive value is not sufficiently high to exclude TBM when the result is negative and it is not a 'ruled out' test [69]. In addition, Xpert Ultra is not widely available in most centres from resource-limited settings. Third, information was scarce in order to perform consistently some subgroup analyses; however, individual data suggest the importance of CSF volume and centrifugation in the accuracy of Xpert MTB/RIF for

**Figure 2** Receiver operating characteristic (ROC) curve for Xpert MTB/RIF diagnostic performance for definite tuberculous meningitis (TBM) (a) and for definite + probable TBM (b). The black curve corresponds to summary ROC. The black emptied circles are sensitivity and specificity estimates per study. The filled blue square is the pooled estimate of sensitivity and specificity obtained from the bivariate model under the assumption that the reference standard is perfect. Dashed blue lines are 95% CI confidence regions (bold) and 95% predictive regions (non-bold). [Colour figure can be viewed at wileyonlinelibrary.com]



TBM diagnosis. Fourth, our results cannot be extrapolated to paediatric patients due to the few available studies including this population.

In conclusion, Xpert MTB/RIF showed high accuracy for the diagnosis of TBM but a negative test does not rule out TBM. In clinical practice, Xpert MTB/RIF adds speed and sensitivity when compared to classic diagnostic methods and commercial nucleic acid amplification techniques of TBM. However, timely introduction of tuberculosis treatment is a key component of the management of patients with clinical suspicion of TBM. More studies and better strategies for rapidly confirming a diagnosis of TBM in children are urgently needed.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Definite TBM: Developed countries ($n$ = 8 studies).

**Figure S2.** Definite TBM: Underdeveloped countries ($n$ = 20 studies).

**Figure S3.** Definite TBM: Centrifuged CSF sample ($n$ = 14 studies).

**Figure S4.** Definite TBM: Non-centrifuged CSF sample ($n$ = 14 studies).

**Figure S5.** Definite TBM and probable TBM: Developed countries ($n$ = 9 studies).

**Figure S6.** Definite TBM and probable TBM: Underdeveloped countries ($n$ = 21 studies).

**Figure S7.** Definite TBM and probable TBM: Centrifuged CSF sample ($n$ = 16 studies).

**Figure S8.** Definite TBM and probable TBM: Non-centrifuged CSF sample ($n$ = 14 studies).

**Corresponding Author** Adrian V. Hernandez, Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, 69 North Eagleville Rd U-3092, Storrs, CT 06269, USA. Tel.: +1-860-972-4468; E-mail: adrian.hernandez-diaz@uconn.edu
Jose E. Vidal, Department of Neurology, Instituto de Infectologia Emílio Ribas, Av. Dr. Arnaldo, 165 – Pacaembu, São Paulo – SP, 01246-900, Brazil. Tel.: +55 11 995888756; E-mail: josevibe@gmail.com