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Research paper

Abbott RealTime MTB and MTB RIF/INH assays for the diagnosis of tuberculosis and rifampicin/isoniazid resistance

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ABSTRACT

Background: The Abbott RealTime MTB (Abbott-RT) and Abbott RealTime MTB RIF/INH Resistance (Abbott-RIF/INH) assays have been introduced for the detection of tuberculosis (TB) and drug-resistant tuberculosis (DR-TB). We performed a systematic review and meta-analysis to assess the accuracy of Abbott-RT and Abbott-RIF/INH for the detection of TB and DR-TB.

Methods: The Ovid MEDLINE, EMBASE, Cochrane and Web of Science databases were searched to identify eligible articles for the systematic review. The pooled analyses were calculated with a bivariate model. Hierarchical summary receiver operating characteristic curves and the area under the curve (AUC) were used to summarize overall diagnostic performance. Deeks' test was performed to evaluate potential publication bias.

Results: For the Abbott-RT assay, 9 studies including 3, 640 patients met the study criteria. The pooled sensitivity of Abbott-RT for detecting TB was 0.96 (95% CI: 0.88–0.99) and specificity was 0.97 (95% CI: 0.93–0.99). For DR-TB, four studies were included to evaluate the diagnosis accuracy of Abbott-RIF/INH. The pooled sensitivity was 0.88 (95% CI, 0.82–0.93) and specificity was 0.99 (95% CI, 0.96–0.99). No publication bias was found.

Conclusion: Both Abbott-RT and Abbott-RIF/INH assays have good sensitivity, specificity and accuracy for the diagnosis of TB and DR-TB.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains one of the leading causes of infection-related mortality worldwide. Globally, there were 10.4 million TB patients and nearly 2.0 million TB deaths in 2016 according to the WHO (World Health Organization, 2017). Drug-resistant tuberculosis (DR-TB) is a challenge to global TB care and prevention, and it remains a major public health concern worldwide. In 2016, there were 600,000 new cases with resistance to rifampicin (RIF), the most effective first-line anti-tuberculosis drug, of which 490,000 had multidrug-resistant TB (MDR-TB), which is defined as drug resistance at least to both isoniazid (INH) and RIF (World Health Organization, 2017). Early diagnoses of TB and DR-TB are important for appropriate therapy and to control the epidemic of TB. However, there are some limitations in current widely used methods, such as the low sensitivity of the acid-fast bacilli smear and the long turn-around time of mycobacterial culture (Hale et al., 2001). Culture-based drug-susceptibility testing is the gold-standard assay for testing resistance, and is usually time-consuming due to the long turnaround time for mycobacterial cultures.

Molecular tests such as Xpert MTB/RIF (Cepheid, Sunnyvale, California, USA) and Genotype MTBDRplus (MTBDRplus; HAIN LifeScience, Nehren, Germany) have been investigated previously to determine the speed and accuracy of their MTB and/or DR-TB detection

Abbreviations: Abbott-RT, Abbott RealTime MTB; Abbott-RIF/INH, Abbott RealTime MTB RIF/INH Resistance; TB, tuberculosis; DR-TB, drug-resistant tuberculosis; MTB, *Mycobacterium tuberculosis*; RIF, rifampicin; INH, isoniazid; MDR-TB, multidrug-resistant TB; TP, true-positives; FP, false-positives; FN, false-negatives; TN, true-negatives; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; SROC, summary receiver operating characteristic; AUC, area under the SROC curve

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(Steingart et al., 2014; Denkinger et al., 2014; World Health Organisation, 2016; Xie et al., 2017). Recently, the Abbott RealTime MTB (Abbott-RT) and Abbott RealTime MTB RIF/INH Resistance (Abbott-RIF/INH) assays have been introduced for detection of TB and DR-TB, respectively(Wang et al., 2016; Vinuesa et al., 2016; Tang et al., 2015; Tam et al., 2017; Scott et al., 2017; Kostera et al., 2016; Hofmann-Thiel et al., 2016; Hinic et al., 2017; Fu et al., 2016; Chen et al., 2015; Ruiz et al., 2017). The Abbott-RT automated assay includes three steps(Tang et al., 2015): first, specimens are inactivated manually by treatment with inactivation reagent at a sample-to-inactivation reagent ratio of 1:3 for 60 min; second, sample preparation including DNA extraction and amplification are performed automatically with the *m*2000sp system; third, detection is performed using the *m*2000rt real-time PCR instrument. MTB positive specimens detected by Abbott-RT are subsequently analyzed by Abbott-RIF/INH for genotypic resistance profiling. Applications of Abbott-RT and Abbott-RIF/INH for detection of TB and RIF/INH resistance have been reported in recent years, but the data are very limited and the sensitivity and specificity of these assays varied in different studies(Wang et al., 2016; Vinuesa et al., 2016; Tang et al., 2015; Tam et al., 2017; Scott et al., 2017; Kostera et al., 2016; Hofmann-Thiel et al., 2016; Hinic et al., 2017; Fu et al., 2016; Chen et al., 2015; Ruiz et al., 2017).

In consideration of the variable results, we conducted this meta-analysis to assess the diagnostic accuracy of Abbott-RT for TB diagnosis and Abbott-RIF/INH for resistance detection.

2. Methods

This meta-analysis was conducted according to the methodology described in the Cochrane Handbook for Diagnostic Test Accuracy Reviews and the Preferred Reporting Items in Systematic Reviews and Meta-Analysis statement (Leeflang et al., 2013; Moher et al., 2010). We developed a protocol before commencing the review, following standard guidelines.

2.1. Search strategy

We searched the MEDLINE, EMBASE, Cochrane and Web of Science databases for articles published up to Jan 1, 2018 to identify studies in which the Abbott-RT and/or Abbott-RIF/INH assays were applied to diagnose TB and/or RIF/INH resistance. The following search terms were used: “Abbott RealTime MTB” OR “Abbott RealTime MTB INH/RIF” OR “Abbott RT” OR “m2000 RealTime MTB” OR “Abbott” AND “tuberculosis” OR “*Mycobacterium tuberculosis*” OR “TB” OR “drug resistance tuberculosis” OR “Multidrug-resistant tuberculosis”. References within selected articles were also reviewed to identify additional relevant studies.

2.2. Inclusion and exclusion criteria

The included studies in this meta-analysis satisfied all the following inclusion criteria: 1) an original research article written in English; 2) the Abbott-RT and/or Abbott-RIF/INH assays were used for the diagnosis of TB and/or DR-TB, and the reference standard was described and acceptable; 3) sufficient data were presented directly or could be calculate indirectly. The exclusion criteria were as follows: 1) review articles, letters, comments, case reports and meta-analyses; 2) studies with fewer than 10 patients.

2.3. Reference standard

For TB, acceptable reference standards were mycobacterial culture positive or a composite reference standard defined by the authors of the independent studies. The composite reference standard might include smear positive, histology or samples originated from known TB patients. For DR-TB, the phenotypic culture-based drug-susceptibility testing method was regarded as the reference standard, as recommended by the WHO(World Health Organization, 2008).

2.4. Data extraction and quality assessment

Titles and abstracts of all studies were independently screened, and full-text publications of relevant articles were read by two investigators (Ming-Gui Wang and Shou-Quan Wu). A third person (Yu Wang) resolved the differences until all arrived at a set of similar statements. Then, the following data were extracted from each study: the first author, published year, country, sample size, specimen types, reference standard, and numbers of true-positives (TP), false-positives (FP), false-negatives (FN), and true-negatives (TN) to construct 2×2 tables. The methodological quality assessment was performed using the validated Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) (Whiting et al., 2011). The QUADAS-2 instrument consists of 4 domains: patient selection, index test, reference standard, and flow and timing.

2.5. Meta-analysis

Meta-analysis was conducted using STATA 14.0 (Stata Corporation: College Station, TX, USA) software. The following data were estimated for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) together with 95% confidence intervals (95% CIs). Sensitivity, also known as true-positive rate (TPR), is the proportion of patients with positive diagnostic tests determined by the gold standard to be positive. The false-negative rate (FNR) means the proportion of patients with negative diagnostic tests determined by the gold standard to be positive. Specificity, also known as true-negative rate (TNR), is the proportion of patients with negative diagnostic tests determined by the gold standard to be negative. The false-positive rate (FPR) means the proportion of patients with positive diagnostic tests determined by the gold standard to be negative. A bivariate model was used to plot the summary receiver operating characteristic (SROC) curve (Reitsma et al., 2005) and then to calculate the area under the SROC curve (AUC). An AUC of 50% would indicate no discriminatory ability, while an AUC of 100% means perfect diagnostic ability (Littenberg and Moses, 1993; Deeks, 2001). A likelihood ratio scattergram was also plotted to estimate the application values of this assay. In addition, the Deeks' funnel plot was generated to detect the potential publication bias (Deeks et al., 2005; Van Enst et al., 2014). This test has been developed specifically for diagnostic test accuracy systematic reviews and plots the natural logarithm of the DOR against the reciprocal of the square root of the effective sample size and tests for asymmetry of this plot. All reported P values were 2 sided and $P < .05$ was considered to be statistically significant.

2.6. Investigation of heterogeneity and sensitivity analysis

Heterogeneity between studies was evaluated using the Q test and I^2 statistics (Higgins and Thompson, 2002). Heterogeneity was defined as a P value $< .05$ or determined using I^2 as follows: 0% to 40%, mild heterogeneity; 30% to 60%, moderate heterogeneity; 60% to 75%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity (Higgins and Green, 2011). To investigate the potential source of heterogeneity, subgroup analyses were performed by the study characteristics such as study designs, specimen types, and smear types (Lijmer et al., 2002). A meta-analysis for a predefined subgroup was only carried out if at least four studies were available. The confidence intervals of individual studies in the forest plots and SROC curves were also visually inspected to investigate heterogeneity. A sensitivity analysis was carried out to analyze the impact of inclusion of specific studies.

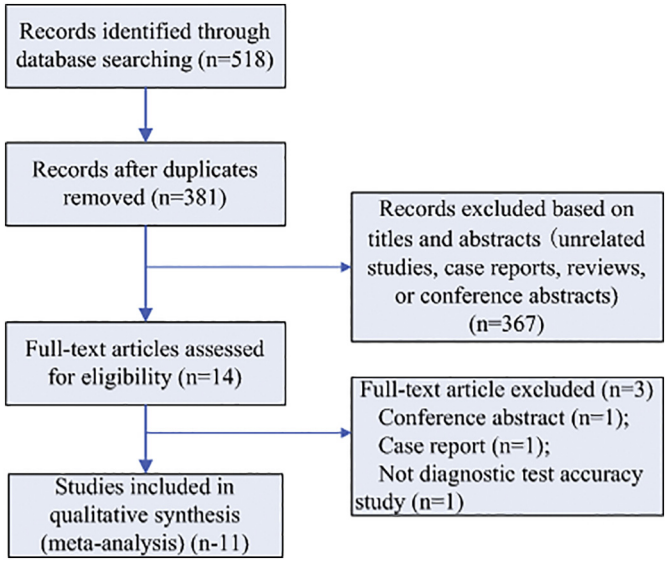

Fig. 1. Flow chart of study selection in this meta-analysis.

3. Results

3.1. Search results and study characteristics

The literature search identified 518 studies and after removal of duplicates 381 studies remained, of which we excluded 367 studies based on titles and abstracts (irrelevant studies and those that were case reports, reviews, or conference abstracts) (Fig. 1). We retrieved full text articles for 14 citations: three were excluded, one because it was published as a conference abstract (Wallis et al., 2016), one because it was a case-report (Morales-Lopez et al., 2017), and another because it was conducted to evaluate the sample inactivation procedure used in the Abbott RT assay (Qi et al., 2015). Finally, 11 studies were included in the current meta-analysis based on the inclusion criteria (Table 1) (Wang et al., 2016; Vinuesa et al., 2016; Tang et al., 2015; Tam et al., 2017; Scott et al., 2017; Kostera et al., 2016; Hofmann-Thiel et al., 2016; Hinic et al., 2017; Fu et al., 2016; Chen et al., 2015; Ruiz et al., 2017). These studies were published between 2015 and 2017 and included a total of 3640 samples. Data came from the People's Republic of China, South Africa, Russia, Uganda, and Vietnam, Switzerland, Germany, Spain and Bangladesh. Nine studies were used to assess the accuracy of Abbott-RT, and four studies were used to evaluate the accuracy of Abbott-RIF/INH. One study included HIV-positive patients (Scott et al., 2017). One study analyzed only the accuracy of drug resistance detection (Kostera et al., 2016). One study regarded culture or histological diagnosis as the reference standard (Fu et al., 2016), and in another study two smear positive specimens originated from known TB patients were considered confirmed TB without mycobacterial culture (Hinic et al., 2017). Seven studies included only respiratory specimens (Table 1) (Wang et al., 2016; Vinuesa et al., 2016; Tang et al., 2015; Tam et al., 2017; Scott et al., 2017; Chen et al., 2015). Four studies described the performance of the Abbott-RT assay in suspected TB samples including respiratory samples and non-respiratory samples.

3.2. Quality assessment

Quality assessments using the QUADAS-2 criteria are summarized in Supplementary Fig. S1 and S2. We judged all the included studies as having low risk of bias for the index test. However, we considered that quality may have been compromised for three reasons: 1) five included studies had a high risk of bias for patient selection (either due to a case-control design, or enrollment by convenience, or both); 2) seven studies had a high risk of bias for flow and timing (two studies used different

Table 1
Characteristics of studies included in the meta-analysis.

Study	Year	Country	Sample size	Case-control study	Specimen type	Reference standard
Chen et al.	2015	China	535	No	Respiratory specimens	Culture
Fu et al.	2016	China	96	Yes	Respiratory specimens and non-respiratory specimens	Culture and composite reference standard
Hinic et al.	2017	Switzerland	287	No	Respiratory specimens and non-respiratory specimens	Culture and composite reference standard
Hofmann-Thiel et al.	2016	Germany	715	Yes	Respiratory specimens and non-respiratory specimens	Culture and phenotypic drug-susceptibility testing
Tang et al.	2015	Russia, South Africa, Uganda, and Vietnam	282	No	Respiratory specimens	Culture
Scott et al.	2017	South Africa	206	No	Respiratory specimens	Culture and phenotypic drug-susceptibility testing
Tam et al.	2017	China	610	No	Respiratory specimens	Culture
Kostera et al.	2016	Russia and Bangladesh	217	No	Respiratory specimens	Phenotypic drug-susceptibility testing
Vinuesa et al.	2016	Spain	257	No	Respiratory specimens	Culture
Wang et al.	2016	China	270	No	Respiratory specimens	Culture
Ruiz et al.	2017	Spain	165	No	Respiratory specimens and non-respiratory specimens	Phenotypic drug-susceptibility testing

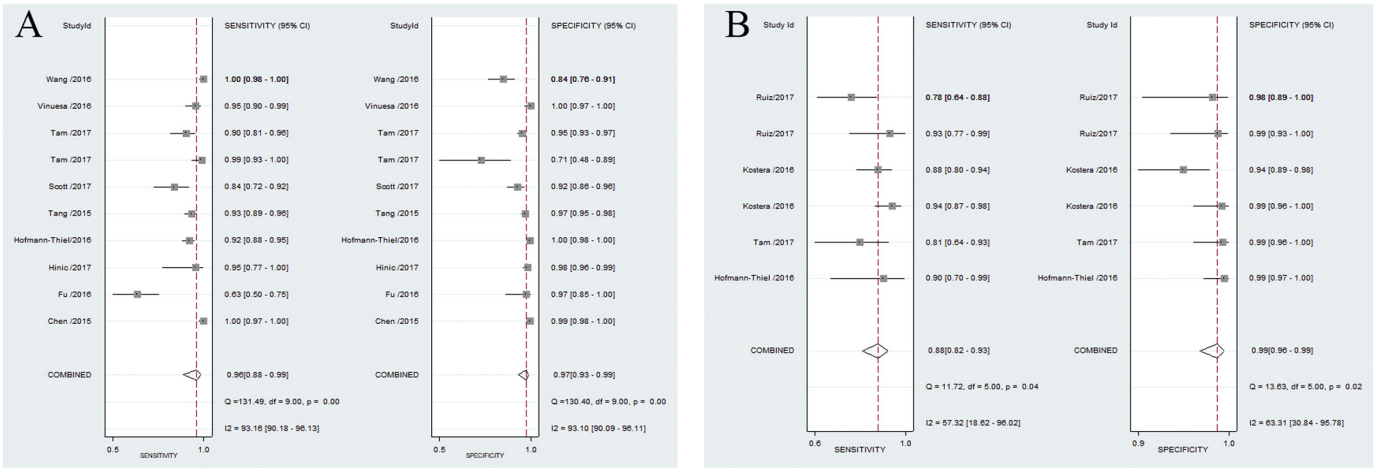

Fig. 2. Analysis of sensitivity and specificity of the Abbott RealTime MTB and Abbott RealTime MTB RIF/INH Resistance assays. Forest plots of sensitivity and specificity of the assays in (A) diagnosing TB and (B) detecting RIF/INH resistance. 95% CI are included between parentheses. (Abbreviations: MTB, *Mycobacterium tuberculosis*; TB, tuberculosis; RIF, rifampicin; INH, isoniazid; CI, confidence interval.)

references, and five studies excluded some patients in the final analysis); 3) one study had potential bias due to the influence of previous knowledge on the interpretation of the reference standard Whiting et al. (2013).

3.3. Diagnostic accuracy of Abbott-RT

Nine studies (Wang et al., 2016; Vinuesa et al., 2016; Tang et al., 2015; Tam et al., 2017; Scott et al., 2017; Hofmann-Thiel et al., 2016; Hinic et al., 2017; Fu et al., 2016; Chen et al., 2015) (3467 samples in total) were included in the meta-analysis to evaluate the accuracy of the Abbott-RT assay. Pooled sensitivity (TPR) for the diagnosis of TB was 0.96 (95% CI, 0.88–0.99) and pooled specificity (TNR) was 0.97 (95% CI, 0.93–0.99) (Fig. 2A). In another words, the FNR was 0.04, and the FPR was 0.03. Additionally, pooled parameters including PLR (34.69, 95% CI, 13.33–90.31), NLR (0.04, 95% CI, 0.02–0.12), and DOR (822, 95% CI, 209–3229) were calculated. The SROC curve with an AUC of 0.99 (Fig. 3A) suggested high overall diagnostic accuracy of the Abbott-RT in detection of TB. There was considerable heterogeneity observed among included studies, with an I^2 value of 93.2% for sensitivity and 93.1% for specificity. As shown in a likelihood ratio scattergram (Supplementary Fig. S3A), the PLR was > 10, while the NLR was < 0.1, which indicated that Abbott-RT can be used as a good method for TB exclusion and confirmation.

Subgroup analyses were performed by study designs, specimen types and smear types, and the results are summarized in Table 2 (Supplementary Fig. S4 and S5). For studies that were not case control designs, high pooled sensitivity 0.97(0.91–0.99) and specificity 0.96(0.90–0.99) estimates were obtained. For the respiratory specimens, the pooled sensitivity and specificity were similar to the overall results, with an AUC of 0.99. Similar results were observed in the smear subgroup. In the smear positive group, substantial heterogeneity was found in sensitivity, with an I^2 value of 73.2%, but only moderate heterogeneity in specificity (I^2 value of 46.6%).

Significant heterogeneity could be detected between studies. We performed sensitivity analysis by omitting one study at a time, but failed to find any specific study that significantly affected the pooled results, indicating good stability of the meta-analysis.

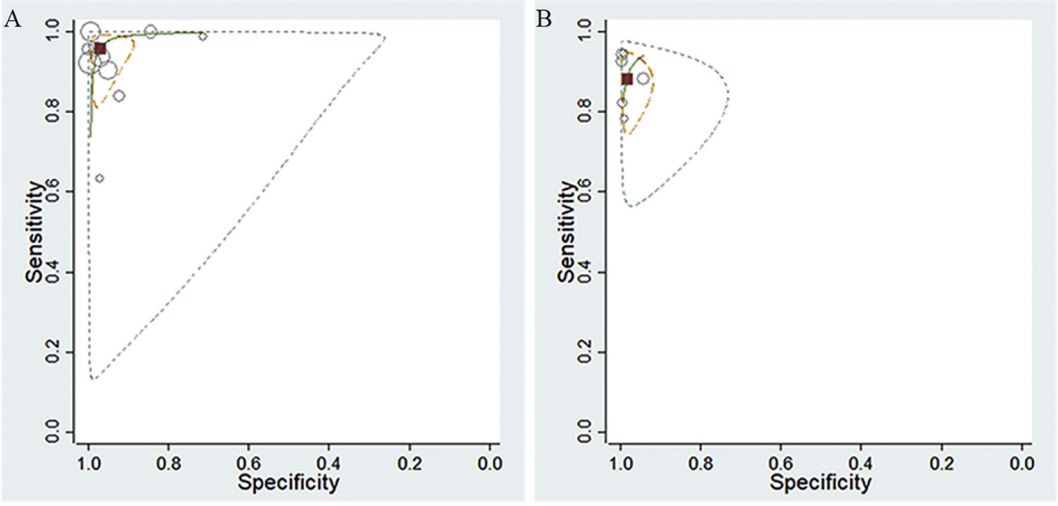

Fig. 3. SROC of the Abbott RealTime MTB assay for the diagnosis of TB (A) and the Abbott RealTime MTB RIF/INH Resistance assay for the detection of RIF/INH resistance (B). The size of each solid circle represents the sample size of each individual study. The summary point is a closed circle, representing sensitivity and specificity estimates pooled with a bivariate random-effects model. (Abbreviations: SROC, summary receiving operation characteristic; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis; RIF, rifampicin; INH, isoniazid; AUC, area under the curve; Se, standard error.)

Table 2
Subgroup analysis of the results of Abbott RealTime MTB for detecting TB.

Variables	Number of studies	Sensitivity (95% CI)	I^2	Specificity (95% CI)	I^2	AUC
Case-control study						
Yes	2	NE	NE	NE	NE	NE
No	7	0.97 (0.91–0.99)	86.6%	0.96 (0.90–0.99)	93.3%	0.99
Respiratory specimens						
Yes	9	0.97 (0.92–0.99)	82.3%	0.97 (0.93–0.99)	93.0%	0.99
No	3	NE	NE	NE	NE	NE
Smear-positive						
Yes	7	0.98 (0.94–0.99)	73.2%	0.70 (0.44–0.87)	46.6%	0.97
No	7	0.90 (0.63–0.98)	93.9%	0.98 (0.94–0.99)	92.6%	0.99

Abbreviations: MTB, *Mycobacterium tuberculosis*; TB, tuberculosis; CI, confidence interval; AUC, the area under the curve; NE, not estimable.

3.4. Diagnostic accuracy of Abbott-RIF/INH

Four studies (Tam et al., 2017; Kostera et al., 2016; Hofmann-Thiel et al., 2016; Ruiz et al., 2017) (972 samples in total) utilizing Abbott-RIF/INH for detection of DR-TB were included in the meta-analysis. Pooled sensitivity (TPR) for the diagnosis of DR-TB was 0.88 (95% CI, 0.82–0.93) and pooled specificity (TNR) was 0.99 (95% CI, 0.96–0.99) (Fig. 2B). In addition, the PLR (60.60, 95% CI, 24.00–152.90), NLR (0.12, 95% CI, 0.08–0.18), and DOR (513, 95% CI, 172–1535) were also calculated. The SROC curves analysis demonstrated excellent overall accuracy with an AUC of 0.98 (Fig. 3B). The Q test and I^2 tests for heterogeneity in the summary results suggested a moderate heterogeneity in sensitivity among included studies, with an I^2 value of 57.3%, while there was a substantial heterogeneity in specificity, with an I^2 value of 63.3%. The likelihood ratio scattergram (Supplementary Fig. S3B) suggested that RIF/INH is an effective technique for detection of DR-TB.

3.5. Publication bias

Deeks' funnel plot asymmetry test was performed to evaluate potential publication bias of the included studies. No evidence for substantial publication bias was found either for Abbott-RT ($P = .28$) or Abbott-RIF/INH assay ($P = .77$), which suggested a low likelihood of publication bias.

4. Discussion

To our knowledge, this systematic review and meta-analysis is the first to examine the diagnostic accuracy of the Abbott-RT and Abbott-RIF/INH assays. Our results demonstrated high sensitivity and specificity of Abbott-RT for TB detection and Abbott-RIF/INH for DR-TB diagnosis. In addition, the AUC of the SROC indicates a good accuracy of the Abbott-RT and Abbott-RIF/INH assays. The findings of this study may enhance the clinical uptake of these assays for the diagnosis of TB and DR-TB.

The key finding of this study is that Abbott-RT is a valuable technique for the diagnosis of TB, with good sensitivity and specificity (higher than 0.95). The high sensitivity and specificity (0.97 and 0.97, respectively) of Abbott-RT in respiratory samples highlight its potential for use in pulmonary TB detection. Unfortunately, as there were fewer than four studies on the diagnosis of extrapulmonary TB, we were unable to evaluate the diagnostic accuracy of Abbott-RT for extrapulmonary TB detection and therefore this issue needs further study. In addition, the evidence presented in this meta-analysis shows that Abbott-RT sensitivity estimates were higher in smear positive (0.98) than in smear negative samples (0.90). However, our results in the smear negative group had a high specificity (0.98), which means that Abbott-RT may be a good diagnostic technique for exclusion of smear negative TB.

Considering the significant heterogeneity among the studies, we performed subgroup analyses to explore the source of the heterogeneity. The smear results were identified as a possible source of heterogeneity. Heterogeneity was significantly decreased among the smear positive group in sensitivity and specificity ($I^2 = 73.2\%$ and 46.6%, respectively). Since we were limited by the number of studies, we unable to perform additional subgroup analyses to identify other causes of the heterogeneity. In addition, our sensitivity analyses showed that the pooled results were relatively stable and not affected by a single study, which means none of the included studies was especially contributing to the heterogeneity.

Abbott-RIF/INH was found to have both a good sensitivity (0.92, 0.86–0.95) and specificity (1.00, 0.68–1.00) for the diagnosis of DR-TB. In the current study, only four studies were included in the analysis of the diagnosis accuracy of DR-TB. Of these studies, two detected the diagnostic accuracy of RIF and INH resistance separately (Kostera et al., 2016; Ruiz et al., 2017), one detected only INH resistance (Tam et al., 2017), while another study detected DR-TB without distinguishing between RIF and INH resistance (Hofmann-Thiel et al., 2016). Even though the number of studies was limited, our results suggest that Abbott-RIF/INH was useful in the diagnosis of DR-TB. However, we were unable to assess the diagnostic accuracy of Abbott-RIF/INH for detection of RIF and INH resistance separately, due to the limited number of studies. We conclude that the Abbott-RIF/INH assay has potential to diagnose RIF and INH resistance after detection of TB, but more research is needed. Significant heterogeneity was also found between studies of the Abbott-RIF/INH assay but the limited number of studies precluded any subgroup analysis to identify the possible source of heterogeneity. In addition, we were unable to evaluate the diagnostic accuracy of INH and RIF resistance separately, which may be a source of heterogeneity.

Several limitations of the current meta-analysis should be considered. First, a relatively small number of studies were included in the analysis, particularly those recording the diagnostic performance of Abbott-RIF/INH for DR-TB. This may have limited the statistical power of the assessment of the Abbott-RIF/INH analysis. Second, we were unable to evaluate the diagnostic accuracy of INH and RIF resistance separately. Third, two case-control studies were included (Hofmann-Thiel et al., 2016; Fu et al., 2016), which may lead to overestimation of accuracy in diagnostic studies. However, our subgroup analysis after excluding the case-control studies showed similar results as the overall analysis, which supports our conclusion. Fourth, Deeks' funnel plot was generated to evaluate the publication bias, and no substantial publication bias was found in this study. However, as the Cochrane Handbook points out, the Deeks' test has low power to detect publication bias when there is heterogeneity in the DOR(Macaskill et al., 2010). Furthermore, sample collection and processing were variable across the studies. Because the heterogeneity of the studies was high, the pooled estimates must be interpreted with caution.

In conclusion, we found Abbott-RT and Abbott-RIF/INH to be a good techniques for the diagnosis of TB and DR-TB, respectively. However, the available data are scarce and more studies on the

accuracy of their diagnosis should be encouraged.

Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Contributions

All authors contributed substantially to the study design, data interpretation, and the writing of the manuscript. Dr. Jian-Qing He contributed to the study design and ran and updated the searches. Ming-Gui Wang and Shou-Quan Wu screened the abstracts, completed full text reviews, data extraction and assessments of quality and bias. Miao-Miao Zhang and Miao Xue contributed to data collection and analysis. Qianqian Liu contributed to data collection. Dr. Andrew J Sandford was responsible for the search strategy. All authors reviewed the manuscript.

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