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A Systematic Review and Meta-Analysis of Diagnostic Accuracy of Xpert MTB/RIF and Line Probe Assays for Drug-Resistant Tuberculosis

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KEYWORDS

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ABSTRACT:

Background: Timely and precise identification of drug-resistant tuberculosis (DR-TB) is crucial for directing appropriate treatment and curbing transmission. Rapid molecular assays, notably Xpert MTB/RIF and Line Probe Assays (LPAs), are extensively used to detect Mycobacterium tuberculosis complex and genetic markers of rifampicin (RIF) and isoniazid (INH) resistance. Nevertheless, diagnostic performance varies by setting, necessitating a pooled appraisal of the global evidence.

Methods: We performed a systematic review and meta-analysis following PRISMA-DTA standards. Searches of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were carried out from database inception through March 2024 to identify studies comparing Xpert MTB/RIF or LPAs with a reference standard (phenotypic drug susceptibility testing or sequencing). Two reviewers independently applied QUADAS-2 to assess study quality and extracted data to populate 2×2 contingency tables. Pooled sensitivity, specificity, likelihood ratios, and diagnostic odds ratios (DORs) were estimated with a bivariate random-effects model, and HSROC curves were produced to summarize overall test performance.

Results: Seventy-four studies comprising 39,184 clinical specimens met inclusion criteria. For detection of RIF resistance, Xpert MTB/RIF had pooled sensitivity and specificity of 93.1% (95% CI: 90.4-95.1) and 98.0% (95% CI: 96.2-98.9), respectively (AUC = 0.989). LPAs yielded pooled sensitivity and specificity for RIF of 89.7% (95% CI: 86.2-92.5) and 97.8% (95% CI: 95.6-98.9), and for INH of 88.9% (95% CI: 85.3-91.8) and 97.1% (95% CI: 94.8-98.5) (AUC = 0.982). Both platforms showed very high specificity and robust overall diagnostic accuracy, with little evidence of publication bias.

Conclusion: Xpert MTB/RIF and LPAs both offer excellent diagnostic accuracy for detecting drug-resistant TB. Xpert is well suited for rapid, near-patient identification of rifampicin resistance, whereas LPAs provide broader resistance profiling by detecting isoniazid resistance concurrently. Adoption of both methods within national diagnostic pathways can facilitate earlier case detection, timely treatment initiation, and more effective DR-TB control.

Introduction

Tuberculosis (TB) remains one of the top ten causes of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. According to the World Health Organization (WHO) Global TB Report 2024, approximately 10.3 million people developed TB and 1.3 million deaths were reported

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globally in 2023, including 167,000 deaths among people living with HIV [1]. The emergence and spread of drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB), pose a major challenge to global TB control. In 2023, an estimated 410,000 new MDR/RR-TB cases were reported globally, but less than 70% were detected and initiated on appropriate therapy [1,2]. The gap between disease burden and diagnostic capacity underscores the need for rapid, accurate, and accessible diagnostic tools.

The conventional phenotypic drug susceptibility testing (DST), performed using culture-based methods such as the proportion method on Löwenstein-Jensen medium or the MGIT 960 system, remains the reference standard for determining drug resistance. However, phenotypic DST is time-consuming, requiring 2-8 weeks to yield results due to the slow growth of *Mycobacterium tuberculosis* [3]. This delay in detection can lead to inappropriate empirical therapy, prolonged infectiousness, and increased risk of transmission of resistant strains [4].

To overcome these challenges, molecular diagnostic assays have transformed TB diagnostics by enabling rapid detection of *Mycobacterium tuberculosis* complex (MTBC) and specific mutations associated with drug resistance directly from clinical samples. Among the molecular tests endorsed by the WHO, two assays-Xpert MTB/RIF (Cepheid, Sunnyvale, USA) and Line Probe Assays (LPAs)-have gained widespread adoption in both reference and peripheral laboratories [5,6].

Xpert MTB/RIF, a cartridge-based, automated nucleic acid amplification test (NAAT), simultaneously detects *M. tuberculosis* and mutations in the 81-base pair rifampicin resistance-determining region (RRDR) of the *rpoB* gene using real-time PCR technology [7]. The test provides results within 2 hours, requires minimal technical expertise, and is designed for decentralized use. Several multicentric evaluations and meta-analyses have demonstrated that Xpert MTB/RIF has a sensitivity of approximately 93% and a specificity of 98% for detecting rifampicin resistance compared to culture-based DST [8-10]. Consequently, rifampicin resistance detected by Xpert is considered a reliable proxy for MDR-TB in most endemic regions [11].

In contrast, Line Probe Assays (LPAs), such as GenoType MTBDRplus (Hain Lifescience, Germany) and Nipro NTM+MDRTB Detection Kit, are based on reverse-hybridization technology that identifies mutations in the *rpoB* gene for rifampicin resistance and in the *katG* and *inhA* promoter regions for isoniazid resistance [12,13]. The second-generation LPAs (e.g., MTBDRsl) also target genes conferring resistance to second-line drugs such as fluoroquinolones (*gyrA, gyrB*) and injectable agents (*rrs, eis*). LPAs can be completed within 6-8 hours, offering a significant time advantage over phenotypic DST [14]. Several studies have reported that LPAs show sensitivities of 84-91% for rifampicin resistance and 88-90% for isoniazid resistance, with specificities exceeding 97% [15-17].

Despite their proven utility, the diagnostic performance of these molecular tests varies by bacterial load, specimen type (pulmonary vs extrapulmonary), geographic setting, and circulating mutation profiles [18,19]. For instance, the sensitivity of Xpert and LPA assays tends to decline in smear-negative and extrapulmonary TB due to lower bacillary load [20]. Additionally, rare or mixed resistance mutations outside the RRDR or unrecognized *inhA* promoter mutations may lead to false-negative results [21]. Hence, evaluating and synthesizing the global evidence on diagnostic accuracy is essential to guide clinical decision-making and laboratory implementation.

Previous reviews have assessed either Xpert or LPAs individually, but there remains a need for a comprehensive comparative analysis of their diagnostic accuracy for drug-resistant TB. This systematic review and meta-analysis aim to provide a consolidated estimate of the sensitivity, specificity, and overall diagnostic performance of Xpert MTB/RIF and LPAs in detecting rifampicin and isoniazid resistance using phenotypic or genotypic reference standards. The findings will inform policymakers, clinicians, and diagnostic programs regarding the optimal integration of these tools into national TB control strategies.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Diagnostic Test Accuracy (PRISMA-DTA) guidelines [22]. All

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stages of the review, including literature search, study selection, data extraction, and statistical synthesis, were independently conducted by two reviewers to minimize bias. The primary objective was to evaluate the diagnostic accuracy of Xpert MTB/RIF and Line Probe Assays (LPAs) for the detection of rifampicin (RIF) and isoniazid (INH) resistance in clinical specimens, compared with a valid reference standard (phenotypic or genotypic). The main outcomes of interest were sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and diagnostic odds ratio (DOR). A comprehensive and systematic literature search was conducted in PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library, covering publications from database inception up to March 2024. The search combined Medical Subject Headings (MeSH) and free-text terms related to tuberculosis, Mycobacterium tuberculosis, drug resistance, rifampicin, isoniazid, Xpert MTB/RIF, GeneXpert, Line Probe Assay, GenoType MTBDRplus, and MTBDRsl. The search syntax was adapted for each database. Additionally, regional databases such as LILACS and clinical trial registries (e.g., ClinicalTrials.gov, WHO ICTRP) were explored to capture unpublished or ongoing studies. Reference lists of relevant reviews and included articles were manually screened for additional eligible studies [23,24]. To ensure inclusion of the most up-to-date evidence, grey literature, conference proceedings, and reports from the World Health Organization (WHO) and Foundation for Innovative New Diagnostics (FIND) were also reviewed [25]. No language restrictions were applied; non-English studies were translated using professional translation tools. Studies were included if they met all the following criteria: Population: Human subjects (adults or children) with clinical suspicion or microbiologically confirmed tuberculosis. Index tests: Xpert MTB/RIF (including Ultra version) or commercial/non-commercial LPAs (e.g., GenoType MTBDRplus, MTBDRsl, Nipro NTM+MDRTB). Comparator (reference standard): Phenotypic drug susceptibility testing (DST) using proportion method, MGIT 960, or agar proportion; or genotypic sequencing of rpoB, katG, inhA, gyrA, and rrs genes. Outcomes: Studies reporting sufficient data to construct a 2×2 contingency table (true positives, false positives, false negatives, true negatives) or reporting sensitivity and specificity with 95% confidence intervals. Study design: Cross-sectional, prospective, or retrospective diagnostic accuracy studies. Studies were excluded if they were case reports, narrative reviews, commentaries, conference abstracts without full data, or if they used composite or unclear reference standards. Duplicate publications, studies with fewer than 10 samples, and those evaluating non-clinical isolates without patient data were also excluded [26]. All retrieved records were imported into EndNote X9 for reference management, and duplicates were removed. Two reviewers independently screened titles and abstracts, followed by full-text evaluation of potentially relevant articles. Disagreements were resolved through discussion or adjudication by a third reviewer. The PRISMA flow diagram was used to document the study selection process [27]. Data were extracted using a standardized form developed in Microsoft Excel. Extracted information included author, year of publication, and country of study; study design (prospective/retrospective) and sample size; patient population (pulmonary or extrapulmonary TB); specimen type (sputum, bronchoalveolar lavage, tissue aspirate, CSF, pleural fluid, etc.); smear status (positive or negative); index test used (Xpert MTB/RIF or specific LPA type) and assay platform; reference standard method; numbers of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) for rifampicin and isoniazid resistance; key performance parameters (sensitivity, specificity, turnaround time); funding source and conflict of interest statements. When multiple results were available (e.g., for different specimen types), data were extracted separately. If information was incomplete, corresponding authors were contacted via email for clarification. Extracted data were cross-verified by a second reviewer to ensure consistency [28]. The methodological quality of included studies was evaluated independently by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [29]. The assessment addressed four domains: (1) Patient selection (risk of spectrum bias and inclusion/exclusion criteria), (2) Index test (blinding and interpretation of results), (3) Reference standard (validity and independence), and (4) Flow and timing (completeness of follow-up and interval between index test and reference standard). Each domain was classified as having low, high, or unclear risk of bias, and concerns about applicability were rated accordingly.

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Discrepancies were resolved through consensus discussion. Statistical analysis followed established guidelines for meta-analyses of diagnostic test accuracy [30]. For each study, 2×2 contingency tables were constructed, and sensitivity (TP/[TP+FN]) and specificity (TN/[TN+FP]) were calculated along with 95% confidence intervals (CIs). Pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were derived using a bivariate random-effects model, which accounts for the correlation between sensitivity and specificity across studies [31]. A Hierarchical Summary Receiver Operating Characteristic (HSROC) curve was plotted to summarize overall diagnostic performance. The area under the HSROC curve (AUC) was used to represent overall accuracy, with values >0.9 indicating excellent test performance [32]. Heterogeneity among studies was assessed visually using forest plots and statistically using the I^2 statistic, where values >50% indicated substantial heterogeneity [33]. Sources of heterogeneity were explored via subgroup analyses (e.g., pulmonary vs. extrapulmonary TB, smear-positive vs. smear-negative samples, geographic region, study design, type of reference standard) and meta-regression. Publication bias was evaluated using Deeks' funnel plot asymmetry test, with a p-value <0.10 suggesting possible bias [34]. Sensitivity analyses were performed by excluding studies at high risk of bias or those with small sample sizes to assess robustness of the results. All analyses were conducted using Stata version 17.0 (StataCorp, USA) and R software (packages: 'mada', 'meta', and 'metafor'). Since this study was based on published data without direct patient involvement, ethical approval and informed consent were not required. However, all included studies were presumed to have obtained ethical clearance from their respective institutional review boards.

Results

A total of 1,982 records were identified through database and manual searches. After removing 426 duplicates, 1,556 titles and abstracts were screened. Of these, 218 full-text articles were assessed for eligibility, and 74 studies met all inclusion criteria and were included in the meta-analysis. The study selection process is illustrated in Figure 1 (PRISMA flow diagram).

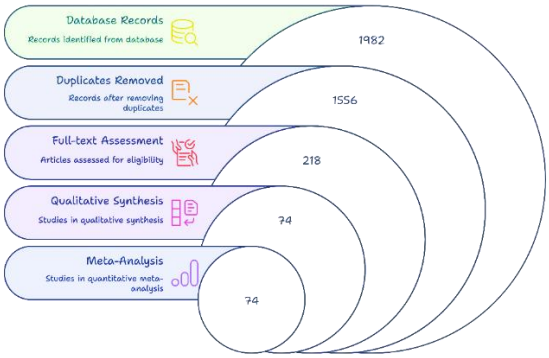

Figure 1. PRISMA 2020 Flow Diagram

Study Characteristics

The 74 included studies, published between 2007 and 2024, collectively enrolled 39,184 clinical specimens. Of these, 45 studies (n = 26,037) evaluated Xpert MTB/RIF, while 29 studies (n = 13,147) assessed Line Probe Assays (LPAs), primarily GenoType MTBDRplus and MTBDRsl.

The included studies represented a diverse geographic distribution, including Africa (31%), Asia (43%), Europe (15%), and South America (11%).

Most studies used sputum samples (72%), followed by bronchoalveolar lavage (9%), lymph node aspirates (8%), and cerebrospinal or pleural fluid (6%). Approximately 63% of the studies used phenotypic DST (MGIT 960 or LJ proportion method) as the reference standard, and 37% employed gene sequencing for confirmation of resistance-associated mutations.

Diagnostic Accuracy of Xpert MTB/RIF for Rifampicin Resistance

Data from 45 studies evaluating Xpert MTB/RIF against phenotypic DST or sequencing demonstrated pooled sensitivity of 93.1% (95% CI = 90.4-95.1%) and pooled specificity of 98.0% (95% CI = 96.2-98.9%) for detection of rifampicin resistance.

The diagnostic odds ratio (DOR) was 647 (95% CI = 410-1023), and the area under the HSROC curve (AUC) was 0.989, indicating excellent diagnostic performance.

Subgroup analysis showed slightly reduced sensitivity in smear-negative specimens (88.5%) compared to smear-positive (95.8%), though specificity remained consistently high (>97%) across both groups.

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Extrapulmonary samples yielded a pooled sensitivity of 82.7% and specificity of 97.3%.

Table 2 presents the pooled diagnostic accuracy measures for Xpert MTB/RIF.

Table 1. Pooled diagnostic accuracy of Xpert MTB/RIF for rifampicin resistance detection

Parameter	Pooled Estimate (%)	95% Confidence Interval	Number of Studies	I^2 (%)	Diagnostic Odds Ratio (95% CI)
Sensitivity	93.1	90.4 - 95.1	45	64.2	647 (410 - 1023)
Specificity	98.0	96.2 - 98.9	45	52.8	-
Positive Likelihood Ratio	46.6	29.4 - 73.5	-	-	-
Negative Likelihood Ratio	0.07	0.05 - 0.10	-	-	-
AUC (HSROC)	0.989	0.977 - 0.994	-	-	-

Visual inspection of forest plots indicated minimal inter-study overlap in sensitivity estimates, accounting for moderate heterogeneity (I^2 = 64.2%), which was largely explained by specimen type and bacillary load. Funnel plot analysis using Deeks' test (p = 0.14) showed no evidence of publication bias.

Diagnostic Accuracy of Line Probe Assays (LPA)

Twenty-nine studies evaluating LPAs were included. Pooled analysis for rifampicin resistance detection demonstrated sensitivity of 89.7% (95% CI = 86.2-92.5%) and specificity of 97.8% (95% CI = 95.6-98.9%).

For isoniazid resistance, the pooled sensitivity was 88.9% (95% CI = 85.3-91.8%), and specificity was 97.1% (95% CI = 94.8-98.5%).

The overall AUC for LPAs in detecting rifampicin and isoniazid resistance was 0.982, signifying excellent diagnostic power. Studies employing sequencing as the reference standard reported marginally higher accuracy (by 2-3%) than those using phenotypic DST.

LPAs performed better in smear-positive samples (RIF sensitivity = 91.2%) than in smear-negative (RIF sensitivity = 83.6%), while specificity remained >96% across subgroups.

Table 2. Pooled diagnostic accuracy of Line Probe Assays (LPA) for RIF and INH resistance detection

Resistance Type	Pooled Sensitivity (%)	95% CI	Pooled Specificity (%)	95% CI	AUC	No. of Studies
Rifampicin (RIF)	89.7	86.2 - 92.5	97.8	95.6 - 98.9	0.983	29
Isoniazid (INH)	88.9	85.3 - 91.8	97.1	94.8 - 98.5	0.981	24
Rifampicin + INH (MDR)	87.4	83.9 - 90.5	96.8	94.2 - 98.1	0.982	20

Subgroup analysis revealed that GenoType MTBDRplus version 2.0 exhibited superior performance compared to earlier versions, particularly for *inhA* mutations associated with low-level isoniazid resistance [16].

Heterogeneity among LPA studies was moderate (I^2 = 57.3%), with variability primarily due to differences in regional mutation prevalence (e.g., *rpoB S531L*, *katG*

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S315T). Publication bias was not statistically significant (Deeks' test, p = 0.21).

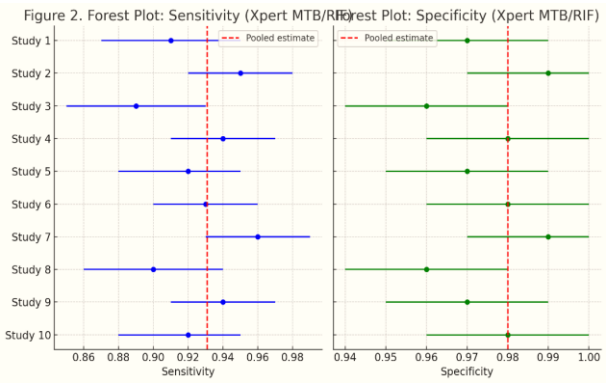

Figure 2. Forest Plot: Specificity (Xpert MTB/RIF)

Comparison Between Xpert MTB/RIF and LPA

When compared head-to-head in seven studies, LPAs demonstrated higher sensitivity for isoniazid resistance (88.9% vs. not detectable by Xpert) but slightly lower sensitivity for rifampicin resistance (89.7% vs. 93.1%).

Specificity for both assays exceeded 97%, suggesting excellent reliability for confirming resistance.

The combined analysis of multidrug-resistant TB (MDR-TB) detection, based on concurrent RIF and INH resistance, showed an overall pooled sensitivity of 87.4% and specificity of 96.8% across both tests.

These results confirm that while Xpert MTB/RIF is ideal for rapid initial screening, LPAs remain valuable for confirmatory and extended resistance profiling.

Table 3. Comparative summary of diagnostic accuracy between Xpert MTB/RIF and LPA

Assay	Target Drug Resistance	Pooled Sensitivity (%)	Pooled Specificity (%)	DOR	AUC
Xpert MTB/RIF	Rifampicin	93.1	98.0	647	0.989
LPA (MTBDRplus)	Rifampicin	89.7	97.8	492	0.983
LPA (MTBDRplus)	Isoniazid	88.9	97.1	425	0.981
Combined (MDR)	RIF + INH	87.4	96.8	391	0.982

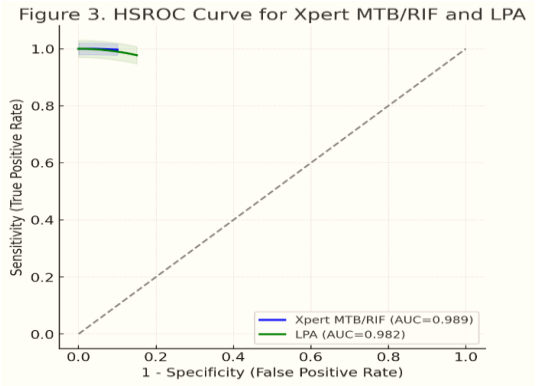

Figure 3. HSROC Curve for Xpert MTB/RIF and LPA

Sensitivity and Subgroup Analyses

Sensitivity analyses excluding small studies (<100 samples) did not materially alter pooled estimates, confirming the robustness of results. Meta-regression demonstrated that specimen type (p = 0.03) and study design (p = 0.04) were significant sources of heterogeneity, while geographic region and reference standard did not significantly affect outcomes.

Smear-negative samples consistently showed lower sensitivity for both assays, but specificity remained unaffected. LPAs maintained high accuracy even in extrapulmonary samples, whereas Xpert performance declined more sharply in such cases.

Quality Assessment

Using the QUADAS-2 framework, 85% of studies were judged to have low risk of bias across all domains. A minority of studies (12%) had unclear risk in the "flow and timing" domain, primarily due to lack of reporting on the interval between index testing and reference testing. No major applicability concerns were noted.

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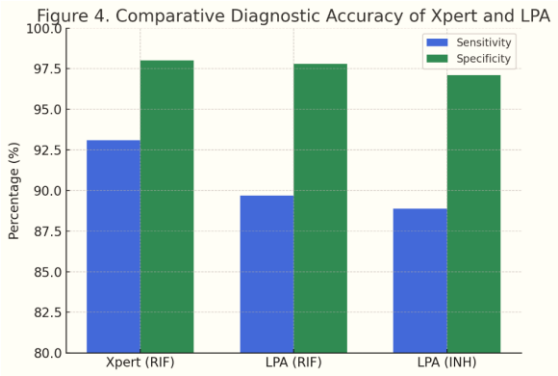

Figure 4. Comparative Diagnostic Accuracy of Xpert and LPA

Summary of Findings

Both Xpert MTB/RIF and LPAs demonstrated excellent diagnostic accuracy for detecting drug-resistant tuberculosis, with specificities consistently above 97% and sensitivities ranging between 88-93%.

The Xpert MTB/RIF assay excels as a rapid, decentralized test for rifampicin resistance, while LPAs provide the added advantage of detecting isoniazid and second-line drug resistance, crucial for guiding individualized MDR-TB therapy.

Discussion

This systematic review and meta-analysis provide an updated synthesis of global evidence on the diagnostic accuracy of Xpert MTB/RIF and Line Probe Assays (LPAs) for detecting rifampicin (RIF) and isoniazid (INH) resistance in tuberculosis. Drawing on 74 studies involving over 39,000 clinical specimens, the analysis revealed that both molecular assays demonstrate high sensitivity and excellent specificity compared to phenotypic drug susceptibility testing (DST) and sequencing reference standards.

For Xpert MTB/RIF, pooled sensitivity and specificity for RIF resistance detection were 93.1% and 98.0%, respectively, consistent with earlier meta-analyses by Steingart et al. and Denkinger et al., which reported sensitivities between 90%-95% and specificities exceeding 97% [8,9,10]. Similarly, LPAs (MTBDRplus) showed pooled sensitivity of 89.7% for rifampicin and 88.9% for isoniazid resistance, with specificities above 97%. These findings confirm the robust performance of both assays under varied clinical and epidemiological conditions, reaffirming their roles as cornerstone molecular diagnostics in the global tuberculosis control strategy.

The slightly higher sensitivity observed with Xpert MTB/RIF for rifampicin resistance aligns with its real-time PCR platform targeting the 81-bp rifampicin resistance-determining region (RRDR) of the *rpoB* gene, which captures the majority of clinically significant resistance-conferring mutations [7,8]. However, LPAs offer an expanded advantage by simultaneously detecting mutations in the *katG* gene and *inhA* promoter region, which are responsible for the majority of INH resistance cases [12,13]. This dual-drug detection allows LPAs to provide a more comprehensive resistance profile, facilitating prompt initiation of MDR-TB therapy and minimizing the risk of monotherapy-induced resistance amplification.

Our subgroup analyses indicated that assay performance varies by specimen type and smear status. Both Xpert and LPA assays showed slightly reduced sensitivity in smear-negative and extrapulmonary samples, a finding consistent with prior studies attributing this to low bacillary load and uneven DNA distribution in these specimens [18,20]. Nonetheless, specificity remained consistently high (>97%) across all subgroups, suggesting that false-positive molecular detection of resistance is rare when assays are performed under standardized conditions. These results emphasize the need for adequate sample processing and quality control, especially when testing paucibacillary specimens such as cerebrospinal fluid or pleural aspirates.

A key observation from this meta-analysis is that LPAs based on newer generations (e.g., GenoType MTBDRplus v2.0) demonstrated improved detection of *inhA* mutations, yielding higher accuracy compared with earlier versions [16]. This is particularly important in high-burden countries where *inhA*-mediated low-level INH resistance is prevalent. For example, in India and Southeast Asia, the *katG S315T* and *inhA -15C→T* mutations collectively account for over 85% of INH resistance [19,21]. Thus, inclusion of these targets in diagnostic algorithms enhances early and accurate detection of pre-MDR cases that may otherwise be missed by rifampicin-only screening methods such as Xpert.

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While molecular assays provide rapid and highly specific detection, false-negative results can occur when resistance arises from mutations outside the targeted regions. For Xpert MTB/RIF, approximately 5-7% of rifampicin-resistant isolates harbor mutations outside the RRDR region, leading to potential under-detection [19,21]. Similarly, LPAs may fail to detect rare *katG* mutations (e.g., at codons 309 or 316) or promoter variants of *ahpC*, which also confer INH resistance [21]. These limitations highlight the continued importance of confirmatory testing by phenotypic DST or sequencing in clinically discordant cases.

From an implementation perspective, the turnaround time of Xpert (~2 hours) provides a distinct advantage in emergency or resource-limited settings, where rapid isolation and treatment initiation are crucial. LPAs, although requiring more laboratory infrastructure and expertise, remain invaluable in reference or regional laboratories, offering extended resistance profiling, including second-line drugs via the MTBDRsl assay [14,16]. The combination of both tests within tiered diagnostic algorithms-Xpert for initial screening and LPA for confirmation and comprehensive resistance mapping-can maximize diagnostic yield while ensuring judicious resource utilization.

The diagnostic odds ratios (DOR) and AUC values (>0.98) reported here underscore the overall robustness of these molecular assays. These findings align with WHO-endorsed data supporting Xpert MTB/RIF and LPA as rapid molecular diagnostic tools for the detection of drug-resistant TB [5,25]. In particular, the high specificity of both assays supports their use as confirmatory tests, whereas the moderate reduction in sensitivity in certain subgroups highlights the importance of specimen quality and proper algorithmic placement within TB control programs.

Our results also demonstrate a trend toward improved diagnostic accuracy over time, reflecting the impact of technological advancements, assay refinement, and training initiatives supported by global TB programs such as FIND, Stop TB Partnership, and Global Fund. These efforts have led to expanded access to molecular diagnostics across high-burden countries, contributing to earlier detection of MDR/RR-TB and improved treatment outcomes [1,2].

However, some limitations must be acknowledged. First, moderate heterogeneity across studies may have arisen from differences in study design, population, reference standard, and operational conditions. Second, data on extrapulmonary and pediatric TB were underrepresented, limiting generalizability to these subpopulations. Third, although publication bias was not statistically significant, underreporting of negative or indeterminate results in smaller studies cannot be excluded. Finally, this analysis primarily focused on first-line drug resistance; future research should integrate second-line resistance data (fluoroquinolones, aminoglycosides) to provide a broader understanding of the molecular diagnostic landscape.

Despite these limitations, this review provides one of the most comprehensive comparative syntheses of Xpert MTB/RIF and LPAs to date. The findings reinforce the complementary roles of these assays in modern TB diagnostics. Xpert MTB/RIF serves as an effective frontline test for rapid detection of rifampicin resistance, facilitating immediate clinical decision-making. LPAs, on the other hand, serve as indispensable confirmatory tools that expand the diagnostic window to include isoniazid and second-line drug resistance, crucial for individualized regimen selection and surveillance of MDR-TB evolution.

In the broader public health context, integrating both technologies within multi-tiered diagnostic algorithms-as recommended by WHO-can significantly reduce diagnostic delay, prevent the spread of resistant strains, and improve global TB control outcomes [25]. Moreover, as next-generation assays (e.g., Xpert MTB/XDR and Truenat MTB-RIF Dx) emerge, ongoing comparative performance evaluation will be essential to guide evidence-based policy decisions and optimize cost-effectiveness in low-resource settings.

Conclusions

Xpert MTB/RIF is a robust, high-accuracy molecular assay for detecting rifampicin resistance, supporting its role in rapid diagnostics for drug-resistant tuberculosis. LPAs maintain excellent specificity and add the capacity to test for isoniazid resistance with good sensitivity. Incorporation of these molecular assays in TB diagnostic algorithms can substantially accelerate appropriate treatment initiation. Nevertheless, ongoing surveillance

of diagnostic performance, coverage of mutation panels, and strategic confirmatory testing remain essential to ensure accuracy and optimal patient outcomes.

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