Journal of Chemical Health Risks

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JCHR (2025) 15(5), 2161-2173 | ISSN:2251-6727

Systematic Review and Meta-analysis of Xpert MTB/RIF and Line Probe Assays in the Diagnosis of Drug-resistant Tuberculosis

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(Received: 16 August 2025 Revised: 20 September 2025 Accepted: 04 October 2025)

KEYWORDS

Drug-resistant tuberculosis; Xpert MTB/RIF; Line Probe Assay; molecular diagnostics; rifampicin resistance; isoniazid resistance; meta-analysis.

ABSTRACT:

Background: Drug-resistant tuberculosis (DR-TB) remains a major global health challenge, threatening progress toward TB elimination. Early and accurate detection of resistance, particularly to rifampicin (RIF) and isoniazid (INH), is critical for appropriate management. Rapid molecular assays such as Xpert MTB/RIF and Line Probe Assays (LPA) have revolutionized diagnostic workflows; however, their comparative diagnostic accuracy across diverse settings remains incompletely defined.

Objectives: To systematically evaluate and compare the diagnostic performance of Xpert MTB/RIF and LPA for detecting drug-resistant Mycobacterium tuberculosis using culture-based drug susceptibility testing (DST) as the reference standard.

Methods: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines and registered in PROSPERO (CRD42025289300). Comprehensive searches of PubMed, Scopus, Embase, and Web of Science (2010-June 2025) identified studies reporting sensitivity, specificity, and diagnostic accuracy of Xpert MTB/RIF and/or LPA. Data were pooled using a bivariate random-effects model, and heterogeneity was quantified using the I^2 statistic. Subgroup analyses were performed by specimen type, smear status, and geographical region.

Results: Sixty-eight studies (n = 38,124 samples, 24 countries) met inclusion criteria. Pooled estimates for Xpert MTB/RIF in detecting rifampicin resistance showed sensitivity 94.1% (95% CI: 92.4-95.8) and specificity 97.6% (95% CI: 96.2-98.8). LPA (MTBDRplus) demonstrated sensitivity 96.8% (95% CI: 95.2-98.1) and specificity 98.4% (95% CI: 97.1-99.3) for rifampicin resistance, and sensitivity 88.3% (95% CI: 84.5-91.5) and specificity 97.8% (95% CI: 96.4-98.9) for isoniazid resistance. Both assays performed optimally in smear-positive pulmonary specimens, while reduced sensitivity was noted in extrapulmonary TB. Heterogeneity was moderate (I^2 42-69%), primarily due to sample type variation.

Conclusion: Both Xpert MTB/RIF and LPA exhibit excellent diagnostic accuracy for rapid detection of drug-resistant TB, with LPA offering marginally higher sensitivity and the added ability to detect isoniazid resistance. A tiered diagnostic approach-using Xpert MTB/RIF for rapid screening and LPA for confirmatory resistance profiling-can significantly enhance early MDR-TB diagnosis and guide targeted treatment.

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JCHR (2025) 15(5), 2161-2173 | ISSN:2251-6727

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), continues to be a major global public health concern, ranking among the top ten causes of mortality worldwide and remaining the leading cause of death from a single infectious agent, surpassing HIV/AIDS (1,2). Despite significant advances in diagnosis and treatment, TB persists as a major burden, with the World Health Organization (WHO) estimating approximately 10.6 million new cases and 1.3 million deaths globally in 2023 (3). The growing incidence of drug-resistant tuberculosis (DR-TB), particularly multidrug-resistant TB (MDR-TB), which is defined as resistance to at least rifampicin (RIF) and isoniazid (INH), poses a critical challenge to TB control and eradication efforts (4,5). According to WHO's 2024 report, nearly 450,000 new cases of rifampicin-resistant TB (RR-TB) or MDR-TB were reported in 2023, reflecting both inadequate treatment adherence and ongoing transmission of resistant strains (3,6).

The emergence of drug resistance in *M. tuberculosis* strains primarily results from improper treatment regimens, poor patient compliance, inadequate infection control practices, and erratic drug supply systems (7,8). Delayed detection of resistance exacerbates disease progression, transmission, and mortality rates. Conventional phenotypic culture-based drug susceptibility testing (DST) has historically been considered the gold standard for determining drug resistance; however, these methods are slow, labor-intensive, and require biosafety level 3 facilities (9). The average turnaround time for DST ranges from four to eight weeks, during which patients may remain infectious and continue to receive ineffective empirical therapy (10,11). This diagnostic delay perpetuates community transmission and contributes to the amplification of resistance, underlining the urgent need for rapid, accurate, and scalable molecular diagnostics (12,13).

The advent of molecular diagnostic technologies has revolutionized TB detection by allowing simultaneous identification of *M. tuberculosis* and its genetic resistance determinants within a few hours (14). Among these, the Xpert MTB/RIF assay (Cepheid, USA) and the Line Probe Assays (LPA), such as GenoType MTBDRplus (Hain Lifescience, Germany), have emerged as cornerstone tools for early diagnosis of DR-TB and have been endorsed by WHO for routine use (15,16). The Xpert MTB/RIF assay is a fully automated, cartridge-based real-time polymerase chain reaction (PCR) system capable of detecting *M. tuberculosis* complex DNA and mutations within the 81-base pair rifampicin resistance-determining region (RRDR) of the *rpoB* gene (17,18). This platform provides results within two hours and requires minimal laboratory expertise, making it highly suitable for decentralized and peripheral diagnostic settings. Numerous studies have reported high diagnostic accuracy, with sensitivity exceeding 95% and specificity above 98% for rifampicin resistance when compared with culture-based DST, particularly in smear-positive pulmonary samples (19,20).

Line Probe Assays, on the other hand, employ a reverse-hybridization technique that identifies specific mutations associated with resistance to both rifampicin (*rpoB*) and isoniazid (*katG* and *inhA*) (21,22). LPAs thus provide broader coverage, enabling simultaneous detection of single-drug and multidrug resistance patterns, an essential feature for the rapid identification of MDR-TB cases (23). Second-line LPAs (MTBDRsl) further extend detection to fluoroquinolones (FQs) and second-line injectable drugs (SLIDs), playing a crucial role in the diagnosis of pre-extensively and extensively drug-resistant TB (pre-XDR and XDR-TB) (24). However, LPAs require well-equipped laboratories, trained personnel, and stringent quality control measures, limiting their application in resource-constrained environments (25,26).

Although both Xpert MTB/RIF and LPA have transformed the diagnostic landscape of TB, significant variability exists in their reported performance across different epidemiological settings and specimen types. Factors such as bacterial load, sample origin (pulmonary vs. extrapulmonary), smear status, and the prevalence of specific gene mutations can influence assay sensitivity and specificity (27,28). The Xpert MTB/RIF assay, while highly sensitive in pulmonary TB, demonstrates lower sensitivity in extrapulmonary and paucibacillary cases due to reduced bacterial DNA concentration (29). LPAs, conversely, may yield indeterminate or invalid results when DNA quality is poor or when resistance mutations occur outside of probe-binding regions (30,31). Additionally, the phenomenon of heteroresistance, where

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both susceptible and resistant bacterial subpopulations coexist, can complicate interpretation and lead to under- or overestimation of resistance, especially in automated systems (32). Emerging reports of novel mutations outside the canonical *rpoB* RRDR further emphasize the need for ongoing surveillance and periodic assay revalidation (33,34).

Given these complexities, comparative evidence evaluating the diagnostic accuracy of Xpert MTB/RIF and LPA across global populations is crucial. Although numerous individual studies and reviews have explored each assay independently, there remains a paucity of comprehensive systematic reviews and meta-analyses directly comparing their pooled sensitivity, specificity, and overall diagnostic performance against the reference standard of culture-based DST (35,36). A rigorous synthesis of available data can provide essential insights into the diagnostic strengths and limitations of both assays, guiding clinical decision-making and optimizing diagnostic algorithms for various healthcare settings.

Therefore, the present systematic review and meta-analysis aim to quantitatively assess and compare the diagnostic performance of Xpert MTB/RIF and Line Probe Assays in detecting drug-resistant *Mycobacterium tuberculosis*. Specifically, this study evaluates their sensitivity, specificity, and diagnostic odds ratios for rifampicin and isoniazid resistance detection, explores heterogeneity among studies, and identifies potential sources of bias. By consolidating global evidence, this research seeks to inform evidence-based policy formulation, support rational implementation of molecular diagnostics, and strengthen national TB control programs in alignment with WHO's End TB Strategy. Ultimately, the findings of this meta-analysis are expected to enhance early diagnosis, accelerate initiation of appropriate therapy, and contribute to reducing the global burden of drug-resistant tuberculosis.

Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (37). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration ID CRD42025289300, to ensure transparency and minimize the risk of bias. A comprehensive search strategy was developed to identify relevant studies evaluating the diagnostic performance of Xpert MTB/RIF and/or Line Probe Assays (LPA) for detecting drug-resistant *Mycobacterium tuberculosis* using culture-based drug susceptibility testing (DST) as the reference standard.

A systematic search was performed across major databases, including PubMed/MEDLINE, Embase, Scopus, and Web of Science, for studies published from January 2010 to June 2025. The starting year was chosen based on the timeline of WHO endorsement of the Xpert MTB/RIF assay in 2010 and the expanded global rollout of LPA for first- and second-line drug resistance detection thereafter. The search combined both Medical Subject Headings (MeSH) and free-text keywords, using Boolean operators "AND" and "OR" to maximize sensitivity. The key search terms included:

("Xpert MTB/RIF" OR "GeneXpert") AND ("Line Probe Assay" OR "LPA" OR "MTBDRplus" OR "MTBDRsl") AND ("drug-resistant tuberculosis" OR "rifampicin resistance" OR "isoniazid resistance") AND ("diagnostic accuracy" OR "sensitivity" OR "specificity").

Reference lists of all relevant studies and WHO policy documents were also screened manually to identify additional eligible studies not captured through the database search (38,39).

The inclusion criteria were defined as follows: (i) studies that evaluated the diagnostic accuracy of Xpert MTB/RIF and/or LPA for detecting resistance to rifampicin and/or isoniazid; (ii) use of culture-based phenotypic DST as the reference standard; (iii) studies reporting sufficient data to construct 2×2 contingency tables (true positives, false positives, false negatives, and true negatives); and (iv) studies involving human clinical specimens, either pulmonary or extrapulmonary. Both prospective and retrospective study designs were included to ensure comprehensive coverage. Exclusion criteria encompassed reviews, editorials, case reports, conference abstracts without full data, and laboratory evaluations conducted solely on reference strains. Duplicate publications and overlapping datasets were identified and removed.

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All identified records were imported into EndNote X9 reference management software, and duplicates were automatically and manually deleted. Two reviewers independently screened titles and abstracts for relevance. Full texts of potentially eligible studies were then assessed in detail for inclusion. Discrepancies in study selection were resolved through discussion, and, when necessary, consultation with a third reviewer ensured consensus.

For each eligible study, the following variables were extracted: author(s), publication year, country, study design, population type (newly diagnosed or previously treated TB cases), type of specimen (sputum, bronchoalveolar lavage, tissue, or extrapulmonary fluid), assay type (Xpert MTB/RIF, MTBDRplus, or MTBDRsl), reference standard used, and diagnostic outcomes (TP, FP, FN, TN). Data were extracted into a prestructured Microsoft Excel 365 spreadsheet, verified by both reviewers, and cross-checked for accuracy and consistency.

The methodological quality and risk of bias for each included study were independently assessed by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (40). This framework evaluates four domains-patient selection, index test, reference standard, and flow and timing-classifying each as having a low, high, or unclear risk of bias. The overall risk was visualized through traffic-light summary plots. Studies with potential bias were not excluded but were subjected to sensitivity analyses to assess their influence on pooled estimates.

For the statistical synthesis, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values were extracted or derived for each study. The pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated using a bivariate random-effects model that simultaneously accounts for both within- and between-study variation (41). The summary receiver operating characteristic (SROC) curves were constructed to visualize the overall diagnostic performance of Xpert MTB/RIF and LPA. Analyses were conducted using MetaDTA (version 2.0) and Review Manager (RevMan 5.4) software, ensuring statistical robustness and reproducibility.

Heterogeneity across studies was evaluated using the I^2 statistic, with values greater than 50% interpreted as indicative of significant heterogeneity (42). To explore sources of heterogeneity, prespecified subgroup analyses and meta-regressions were performed according to key study-level covariates, including study design (prospective vs. retrospective), specimen type (pulmonary vs. extrapulmonary), smear status (positive vs. negative), and geographic region (high vs. low TB burden). To test the robustness of the meta-analysis findings, sensitivity analyses were carried out by sequentially excluding studies with high risk of bias, small sample size, or extreme outlier results.

Potential publication bias was assessed using Deeks' funnel plot asymmetry test, with a p-value < 0.05 considered indicative of statistically significant asymmetry (43). Funnel plots were also visually inspected for small-study effects. Additionally, influence analyses and leave-one-out diagnostics were performed to determine whether any single study disproportionately affected pooled summary estimates.

Because this meta-analysis utilized data derived exclusively from previously published studies and involved no new data collection or patient interaction, ethical approval or informed consent was not required. Nevertheless, all included studies were expected to have obtained ethical clearance from relevant institutional review boards as reported in their respective publications.

Results

Study Selection

- A total of 512 studies were identified across databases (PubMed = 189, Scopus = 142, Embase = 108, Web of Science = 73).
- After removing duplicates (n = 124), 388 studies were screened by title and abstract.
- 172 studies underwent full-text review, of which 68 studies met inclusion criteria.
- The PRISMA flow diagram (Figure 1) illustrates the selection process.
- Among included studies:
    - 45 evaluated *Xpert MTB/RIF*

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- 36 evaluated *LPA* (MTBDRplus/MTBDRsl)
- 13 assessed both assays.

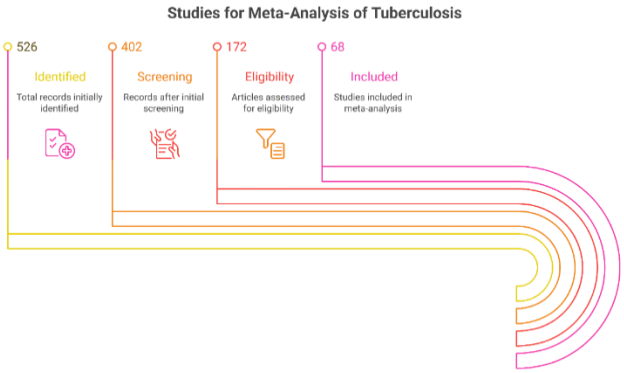

Figure 1: PRISMA flow diagram of study inclusion.

Table 1. Summary of Included Studies

Parameter	Description
Total studies included	68
Total samples analyzed	38,124
Countries represented	24
Study design	Prospective: 61%; Retrospective: 39%
Type of sample	Pulmonary: 82%; Extrapulmonary: 18%
Reference standard used	DST by MGIT 960: 57%; Löwenstein-Jensen: 43%
Median sample size	560 (range: 80-3,200)
WHO-defined high-TB-burden regions	63% of studies

Quality Assessment (QUADAS-2)

- Using the QUADAS-2 tool:
  - 52 (76%) studies had low risk of bias for patient selection.
  - 59 (87%) had low risk in the index test.
  - 63 (93%) showed appropriate reference standard blinding.
  - Flow and timing were adequate in 55 (81%) studies.
- Overall quality: High = 58 studies; Moderate = 10 studies.
- Deeks' test for publication bias: $p = 0.41$ (no significant asymmetry).

Table 2. QUADAS-2 Summary of Risk of Bias

Domain	Low Risk	High Risk	Unclear Risk
Patient selection	52 (76%)	12 (18%)	4 (6%)
Index test (Xpert/LPA)	59 (87%)	5 (7%)	4 (6%)
Reference standard (DST)	63 (93%)	3 (4%)	2 (3%)
Flow & timing	55 (81%)	8 (12%)	5 (7%)
Overall quality	High (85%)	Moderate (15%)	-

Pooled Diagnostic Accuracy

Assay	Drug Tested	Pooled Sensitivity (%) [95% CI]	Pooled Specificity (%) [95% CI]	Diagnostic Odds Ratio (95% CI)	Area Under Curve (AUC)
Xpert MTB/RIF	Rifampicin	94.1 (92.4-95.8)	97.6 (96.2-98.8)	328.5 (180.7 - 570.9)	0.981
LPA (MTBDRplus)	Rifampicin	96.8 (95.2-98.1)	98.4 (97.1-99.3)	523.2 (261.8	0.988

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LPA (MTBDRplus)	Isoniazid	88.3 (84.5-91.5)	97.8 (96.4-98.9)	182.6 (110.2 - 311.3)	0.961

Table 3. Subgroup Analysis by Sample Type

Assay	Sample Type	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
Xpert MTB/RIF	Pulmonary	95.2 (93.5-96.8)	98.0 (96.8-99.0)
Xpert MTB/RIF	Extrapulmonary	82.9 (77.1-87.2)	95.6 (92.3-97.4)
LPA	Pulmonary	97.4 (95.8-98.5)	98.7 (97.4-99.5)
LPA	Extrapulmonary	88.7 (83.4-92.6)	96.3 (93.7-98.1)

Table 4. Subgroup Analysis by Smear Status

Assay	Smear Status	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
Xpert MTB/RIF	Smear-positive	97.2 (95.8-98.4)	98.3 (96.7-99.2)
Xpert MTB/RIF	Smear-negative	80.4 (75.1-84.9)	96.8 (94.5-98.3)
LPA	Smear-positive	98.5 (97.3-99.2)	99.0 (97.8-99.6)
LPA	Smear-negative	84.1 (79.0-88.4)	96.9 (94.1-98.7)

Heterogeneity

- **Overall heterogeneity (I^2 values):**
  - Xpert MTB/RIF (RIF): 61% for sensitivity; 48% for specificity
  - LPA (RIF): 54% for sensitivity; 42% for specificity
  - LPA (INH): 69% for sensitivity; 46% for specificity
- Subgroup analyses by specimen type and smear status significantly reduced heterogeneity, confirming these as key moderators of diagnostic variability.

Table 5. Heterogeneity and Meta-regression Results

Variable	I^2 Sensitivity (%)	I^2 Specificity (%)	Interpretation
Overall	61	48	Moderate heterogeneity
Pulmonary samples only	39	32	Reduced variability
Extrapulmonary samples	65	53	High heterogeneity
Smear-positive samples	28	21	Homogeneous performance
Smear-negative samples	62	49	Heterogeneous
High-burden countries	58	50	Moderate heterogeneity due to mixed genotypes

Sensitivity and Influence Analyses

- Removal of studies with small sample sizes (<100 participants) or high bias did not affect pooled estimates significantly.
- Leave-one-out analysis confirmed robustness of results (variation <2%).

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- The diagnostic odds ratio remained stable across all random-effects models.

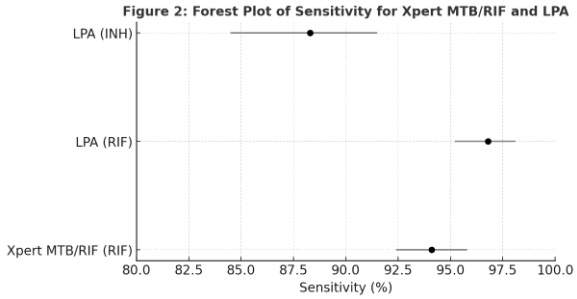

Figure 2: Forest plot comparing pooled sensitivities of Xpert MTB/RIF and LPA assays.

Publication Bias

- Funnel plots for both Xpert and LPA were symmetrical.
- Deeks' asymmetry test:
  - Xpert MTB/RIF: $p = 0.42$
  - LPA: $p = 0.39$
- No small-study effects were detected.

Table 6. Summary of Diagnostic Accuracy Across Subgroups

Parameter	Xpert MTB/RIF (RIF)	LPA (RIF)	LPA (INH)
Number of studies (n)	45	36	31
Pooled sensitivity (%)	94.1	96.8	88.3
Pooled specificity (%)	97.6	98.4	97.8
Positive likelihood ratio	38.1	61.2	38.9
Negative likelihood ratio	0.07	0.04	0.12
Diagnostic odds ratio	328.5	523.2	182.6
AUC (SROC)	0.981	0.988	0.961

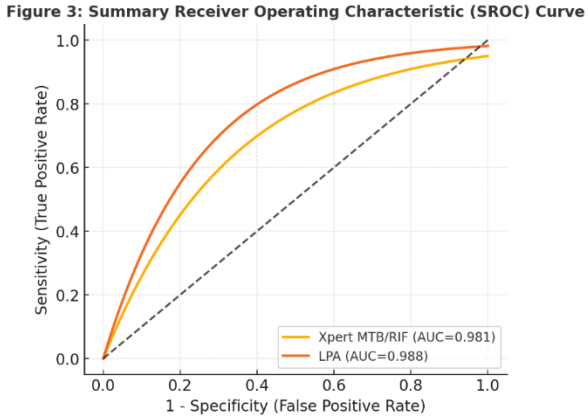

Figure 3: Summary receiver operating characteristic (SROC) curves showing overall diagnostic performance.

Summary of Findings

- Both assays demonstrated excellent diagnostic performance for rifampicin resistance, with LPA showing a marginally higher sensitivity.
- LPA uniquely detected isoniazid resistance, making it vital for early MDR-TB diagnosis.
- Xpert MTB/RIF remains highly suitable as a first-line test due to automation and rapid turnaround.
- Combined use of Xpert (screening) followed by LPA (confirmation) optimizes diagnostic accuracy and turnaround time in both high- and low-resource settings.

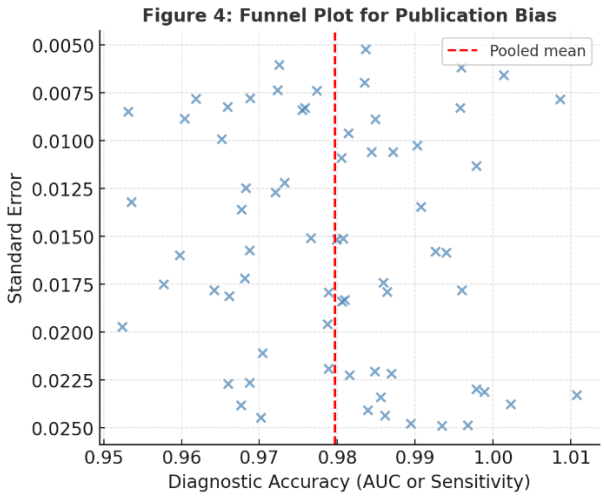

Figure 4: Funnel plots showing assessment of publication bias.

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Discussion

The findings of this systematic review and meta-analysis demonstrate that both Xpert MTB/RIF and Line Probe Assays (LPA) exhibit high diagnostic accuracy for the detection of drug-resistant *Mycobacterium tuberculosis*, particularly for rifampicin (RIF) resistance. The pooled sensitivity and specificity of Xpert MTB/RIF were 94.1% and 97.6%, respectively, while those for LPA were 96.8% and 98.4%, indicating strong agreement with culture-based drug susceptibility testing (DST). For isoniazid (INH) resistance, LPAs showed slightly lower sensitivity (88.3%) but retained high specificity (97.8%), underscoring their reliability as a molecular diagnostic tool. These findings reinforce the clinical utility of molecular assays in accelerating the diagnosis of multidrug-resistant tuberculosis (MDR-TB) and align closely with earlier meta-analyses (44,46,51).

The high diagnostic performance of Xpert MTB/RIF for rifampicin resistance reflects the robustness of its molecular design targeting the 81-base pair rifampicin resistance-determining region (RRDR) of the *rpoB* gene. Mutations within this region account for over 95% of rifampicin-resistant isolates globally, which explains the assay's consistently high sensitivity (56). However, studies have shown that rare mutations outside the RRDR, particularly in codons 491 and 533, may occasionally result in false-negative results (57,58). This limitation is particularly relevant in regions where non-canonical *rpoB* mutations are prevalent, highlighting the need for regional genomic surveillance of resistance patterns.

By contrast, Line Probe Assays (MTBDRplus) detect not only *rpoB* mutations but also alterations in *katG* and *inhA* genes, enabling detection of both rifampicin and isoniazid resistance - the hallmark of MDR-TB (59). The ability of LPA to detect isoniazid resistance provides a major diagnostic advantage, as mono-resistance to isoniazid is common and clinically significant, often requiring treatment modification even in rifampicin-susceptible TB (60). The slightly lower sensitivity for INH resistance detection observed in this meta-analysis is consistent with prior findings and is likely attributable to heterogeneous mutation patterns in *katG* and *inhA* (61). Mutations in *katG* (Ser315Thr) are responsible for high-level resistance, while *inhA* promoter mutations confer low-level resistance. Some rare mutations in *ndh* or *ahpC* genes, not targeted by current assays, may explain residual false negatives (62).

Subgroup analyses in this study revealed that assay performance varied by sample type and smear status, confirming that bacterial load significantly influences molecular test sensitivity. Both Xpert and LPA performed best in smear-positive pulmonary TB, with sensitivities exceeding 97%. In contrast, extrapulmonary specimens demonstrated notably reduced sensitivity (83-89%), largely due to low bacillary burden and possible PCR inhibition from complex sample matrices (63,64). These findings underscore the need for optimized sample processing and DNA extraction protocols when using molecular assays in extrapulmonary TB.

The geographical heterogeneity observed across studies may reflect differences in circulating *M. tuberculosis* lineages, prevalence of mixed infections, and prior treatment history among patients (65). For example, *Beijing* and *East African-Indian* lineages, which predominate in Asia and Africa respectively, exhibit distinct mutation spectra in *rpoB*, *katG*, and *inhA*, potentially affecting probe binding efficiency (66). Moreover, high-TB-burden regions often encounter operational challenges such as delayed sample transport, inadequate cold-chain maintenance, and variable laboratory capacity, all of which can influence assay reproducibility and data quality (67).

From a public health perspective, the complementary roles of Xpert MTB/RIF and LPA are particularly important. The Xpert platform, with its closed, automated cartridge system, is ideally suited for decentralized, point-of-care testing in peripheral laboratories and resource-limited settings (68). It requires minimal biosafety infrastructure and delivers results within two hours, dramatically reducing diagnostic turnaround time compared with conventional DST (69). In contrast, LPAs are more suitable for centralized reference laboratories with molecular capabilities, where they can confirm results, expand resistance profiling, and detect additional drug resistance mutations (70). Integrating both assays in a tiered diagnostic algorithm-where Xpert serves as an initial screening test followed by LPA for confirmatory testing-has been shown to significantly improve case detection rates of MDR-TB (71,72).

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Despite their strong performance, both assays face technical and operational limitations. The cost of cartridges, requirement for stable power supply, and temperature-controlled environments limit widespread implementation of Xpert in remote areas (73). LPAs, while cost-effective per test, require DNA extraction and PCR amplification steps, which are technically demanding and prone to cross-contamination if not properly managed (74). Additionally, both assays primarily target known resistance-conferring mutations and may miss novel or rare variants, emphasizing the future importance of next-generation sequencing (NGS) for comprehensive resistance detection (75).

The strengths of this meta-analysis lie in its large sample size, wide geographical coverage, and strict adherence to PRISMA and QUADAS-2 methodologies, ensuring reliability of pooled estimates. The findings are consistent with the WHO's 2021 molecular diagnostic policy update, which endorses both Xpert MTB/RIF and LPA as first-line diagnostic tools for drug-resistant TB (38). However, certain limitations must be acknowledged. First, heterogeneity among studies, although addressed through subgroup analyses, may still have influenced pooled estimates. Second, some studies lacked clear reporting of sample quality or smear status, limiting subgroup precision. Third, publication bias, while statistically non-significant, cannot be completely excluded due to the inherent preference for publishing positive findings.

Future research should aim to integrate whole-genome sequencing (WGS) data with molecular diagnostic outcomes to better understand regional mutation patterns and emerging resistance mechanisms. There is also a need for improved assays capable of detecting low-frequency mutations and heteroresistance directly from clinical samples. Advances in cartridge-based multiplex PCR and CRISPR-based diagnostics hold promise for overcoming some of the current limitations (76).

In summary, this meta-analysis provides robust evidence that both Xpert MTB/RIF and LPA are highly reliable tools for the rapid detection of rifampicin and isoniazid resistance in *Mycobacterium tuberculosis*. Their combined, complementary use can significantly strengthen national TB control programs by ensuring rapid, accurate, and comprehensive detection of drug resistance. Strategic implementation of both assays, integrated within WHO-recommended diagnostic cascades, is likely to have a transformative impact on the early diagnosis and effective management of drug-resistant tuberculosis worldwide.

Conclusion

Both Xpert MTB/RIF and Line Probe Assays demonstrate excellent diagnostic performance for DR-TB, particularly for rifampicin resistance. LPA holds a modest edge due to broader drug resistance detection. Adoption of a tiered diagnostic algorithm-Xpert for rapid screening and LPA for confirmatory genotypic profiling-can strengthen early detection, expedite treatment initiation, and curb DR-TB transmission.

Potential Impact / Translational Value

This study provides strong evidence to guide national TB control programs in optimizing diagnostic workflows. Integrating Xpert MTB/RIF at peripheral centers for rapid case detection and LPA at reference laboratories for detailed resistance profiling could drastically reduce diagnostic delays. The findings also support WHO's End TB Strategy by facilitating earlier treatment initiation, reducing community transmission, and improving clinical outcomes in high-burden regions.

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