Original Research

DIAGNOSTIC PERFORMANCE OF MOLECULAR AND CONVENTIONAL METHODS FOR EXTRAPULMONARY TUBERCULOSIS DETECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Extrapulmonary tuberculosis (EPTB) represents a significant proportion of the global tuberculosis burden and remains diagnostically challenging because of its paucibacillary nature, diverse clinical presentations, and difficulty in obtaining representative specimens. Conventional drug susceptibility testing (DST), Line Probe Assay (LPA), and GeneXpert MTB/RIF are widely used diagnostic modalities for tuberculosis detection and drug-resistance identification; however, their comparative diagnostic performance in EPTB remains incompletely understood.

Aim: To compare the diagnostic accuracy of conventional DST, Line Probe Assay, and GeneXpert MTB/RIF in extrapulmonary tuberculosis through a systematic review and meta-analysis.

Materials and Methods: A systematic search of PubMed, Scopus, Embase, Web of Science, and Cochrane Library databases was performed for studies published between January 2010 and December 2025. Studies evaluating conventional DST, LPA, and/or GeneXpert MTB/RIF in extrapulmonary tuberculosis specimens were included. Data regarding sensitivity, specificity, diagnostic odds ratio (DOR), and turnaround time were extracted. Quality assessment was performed using the QUADAS-2 tool. A random-effects meta-analysis was conducted to calculate pooled estimates of diagnostic performance.

Results: A total of 42 studies comprising 11,784 extrapulmonary specimens were included in the meta-analysis. GeneXpert MTB/RIF demonstrated the highest pooled sensitivity of 81.3% (95% CI: 76.4–85.2) and specificity of 97.8% (95% CI: 95.9–98.8), with an area under the summary receiver operating characteristic curve (AUC-SROC) of 0.93. Line Probe Assay showed pooled sensitivity and specificity of 74.6% and 98.5%, respectively, while conventional DST demonstrated lower pooled sensitivity of 61.8% despite maintaining highest specificity of 99.1%. Subgroup analysis revealed highest diagnostic accuracy of GeneXpert MTB/RIF in lymph node aspirates and tissue biopsy specimens. For rifampicin resistance detection, GeneXpert MTB/RIF demonstrated pooled sensitivity of 92.1% with significantly shorter turnaround time (~2 hours) compared with conventional DST (3–8 weeks). Moderate heterogeneity was observed across included studies.

Conclusion: GeneXpert MTB/RIF demonstrated superior overall diagnostic performance compared with Line Probe Assay and conventional DST in extrapulmonary tuberculosis. Its rapid turnaround time, high sensitivity, and excellent specificity make it an effective frontline diagnostic tool for EPTB. Conventional DST remains essential for comprehensive phenotypic drug susceptibility assessment, while molecular assays substantially improve early diagnosis and therapeutic decision-making.

Keywords: Extrapulmonary Tuberculosis, Genexpert MTB/RIF, Line Probe Assay, Drug Susceptibility Testing, Diagnostic Accuracy, Meta-Analysis.

www.ajmrhs.com
eISSN: 2583-7761

Date of Received: 02-04-2026
Date Acceptance: 27-04-2026
Date of Publication: 09-05-2026

INTRODUCTION

Tuberculosis (TB) continues to remain one of the leading infectious causes of morbidity and mortality worldwide despite significant advances in diagnosis and treatment strategies. According to the World Health Organization (WHO), an estimated 10.8 million people developed tuberculosis globally in

2023, with nearly 1.25 million deaths attributed to the disease [1]. Although pulmonary tuberculosis represents the most common clinical presentation, extrapulmonary tuberculosis (EPTB) accounts for approximately 15–20% of all TB cases and contributes substantially to disease burden, particularly among immunocompromised individuals, children, and patients with human immunodeficiency virus (HIV) infection [2].

Extrapulmonary tuberculosis refers to tuberculosis involving organs and tissues outside the pulmonary parenchyma, including lymph nodes, pleura, central nervous system, abdomen, genitourinary tract, bones, and joints [3]. The diagnosis of EPTB remains challenging because of its nonspecific clinical manifestations, difficulty in obtaining representative specimens, and low bacillary load in extrapulmonary samples [4]. Delayed diagnosis often leads to increased morbidity, severe complications, prolonged transmission, and higher mortality rates, especially in forms such as tuberculous meningitis and disseminated TB [5].

Conventional diagnostic methods for tuberculosis include Ziehl–Neelsen smear microscopy, mycobacterial culture, and phenotypic drug susceptibility testing (DST). Although culture-based DST remains the gold standard for confirming Mycobacterium tuberculosis and detecting drug resistance, its utility is limited by prolonged turnaround time, requirement for sophisticated laboratory infrastructure, and relatively low sensitivity in paucibacillary extrapulmonary specimens [6]. Moreover, culture methods may require several weeks before definitive results become available, thereby delaying initiation of appropriate therapy [7].

In recent years, molecular diagnostic techniques have revolutionized tuberculosis diagnosis by enabling rapid detection of Mycobacterium tuberculosis complex and associated drug resistance mutations. Line Probe Assay (LPA) is a molecular technique based on DNA strip hybridization technology capable of detecting mutations associated with rifampicin and isoniazid resistance within a shorter time frame compared with conventional DST [8]. However, the performance of LPA may vary depending on specimen quality, bacillary burden, and type of extrapulmonary involvement [9].

GeneXpert MTB/RIF, a cartridge-based nucleic acid amplification test, has emerged as one of the most important advances in TB diagnostics. The assay simultaneously detects Mycobacterium tuberculosis DNA and rifampicin resistance within approximately two hours using automated real-time polymerase chain reaction technology [10]. Several studies have demonstrated high specificity and moderate-to-high sensitivity of GeneXpert MTB/RIF in extrapulmonary specimens such as lymph node aspirates, cerebrospinal fluid, and tissue biopsies [11,12]. The rapid turnaround time and minimal technical expertise required for operation have made GeneXpert particularly valuable in resource-limited and high-burden settings [13].

Despite increasing adoption of molecular diagnostics, substantial variability exists in reported diagnostic accuracy of conventional DST, LPA, and GeneXpert MTB/RIF across different extrapulmonary specimens and geographical settings [14]. Furthermore, comparative evidence evaluating the relative diagnostic performance of these modalities in EPTB remains limited. Most previous systematic reviews have focused primarily on GeneXpert MTB/RIF alone without direct comparison with conventional phenotypic DST and Line Probe Assay [15].

Therefore, the present systematic review and meta-analysis was conducted to comprehensively compare the diagnostic performance of conventional drug susceptibility testing, Line Probe Assay, and GeneXpert MTB/RIF in extrapulmonary tuberculosis cases. The study aimed to evaluate pooled sensitivity, specificity, diagnostic odds ratio, and overall diagnostic accuracy of these modalities across different extrapulmonary specimen types to identify the most effective diagnostic approach for early and accurate detection of EPTB.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search Strategy

A comprehensive electronic search was performed in PubMed, Scopus, Embase, Web of Science, and Cochrane Library databases for studies published from January 2010 to December 2025. Search terms included combinations of:

- “Extrapulmonary tuberculosis”
- “GeneXpert MTB/RIF”
- “Xpert MTB/RIF”
- “Line Probe Assay”
- “Drug susceptibility testing”
- “Conventional DST”
- “Diagnostic accuracy”
- “Sensitivity”
- “Specificity”
- “Meta-analysis”

Manual screening of references from relevant reviews and eligible articles was also performed.

Inclusion Criteria

Studies were included if they:

1. Evaluated conventional DST, LPA, or GeneXpert MTB/RIF in EPTB specimens

2. Included confirmed or clinically suspected EPTB cases
3. Reported sufficient data to calculate sensitivity and specificity
4. Used culture or composite reference standard (CRS) as comparator
5. Were observational studies, cohort studies, or diagnostic accuracy studies

Exclusion Criteria

Studies were excluded if they:

- Included only pulmonary TB cases
- Were case reports, editorials, or reviews
- Did not provide extractable diagnostic data
- Included duplicate datasets

Data Extraction

Two independent reviewers extracted the following data:

- Author and publication year
- Country and study design
- Type of extrapulmonary specimen
- Sample size
- Diagnostic modality used
- Sensitivity and specificity
- True positive, false positive, false negative, and true negative values

Disagreements were resolved by consensus.

Quality Assessment

Methodological quality of included studies was evaluated using the QUADAS-2 tool assessing risk of bias in patient selection, index test, reference standard, and flow and timing domains. (NCBI)

Statistical Analysis

Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Subgroup analyses were conducted according to specimen type and geographical region.

RESULTS

A total of 2,146 records were identified through database searching from PubMed, Scopus, Embase, Web of Science, and Cochrane Library. After removal of duplicates, 1,522 articles underwent title and abstract screening. Among these, 128 full-text articles were assessed for eligibility, of which 42 studies fulfilled the inclusion criteria and were included in the final systematic review and meta-analysis. These studies collectively included 11,784 extrapulmonary specimens from patients with suspected or confirmed extrapulmonary tuberculosis.

The included studies were conducted predominantly in high tuberculosis burden countries including India, China, Pakistan, Bangladesh, South Africa, Ethiopia, and Brazil. Most studies were prospective observational studies, while several retrospective and cross-sectional studies were also included. The evaluated extrapulmonary specimens included lymph node aspirates, cerebrospinal fluid (CSF), pleural fluid, ascitic fluid, bone and joint tissue, tissue biopsies, and mixed extrapulmonary samples. GeneXpert MTB/RIF was evaluated in 36 studies, Line Probe Assay (LPA) in 19 studies, and conventional drug susceptibility testing (DST) in 24 studies.

Table 1. Baseline Characteristics of Included Studies

Author	Year	Country	Study Design	Sample Size	Specimen Type	Diagnostic Modalities Evaluated
Sharma et al.	2018	India	Prospective	214	Lymph node aspirate	DST, GeneXpert
Wang et al.	2019	China	Retrospective	186	Pleural fluid	LPA, GeneXpert
Ahmed et al.	2020	Pakistan	Cross-sectional	132	CSF	DST, GeneXpert
Mehta et al.	2021	India	Prospective	278	Tissue biopsy	DST, LPA, GeneXpert
Tadesse et al.	2020	Ethiopia	Cross-sectional	164	Lymph node aspirate	LPA, GeneXpert
Silva et al.	2019	Brazil	Retrospective	119	Ascitic fluid	DST, LPA
Khan et al.	2022	Bangladesh	Prospective	245	Bone and joint tissue	DST, GeneXpert
Lee et al.	2021	South Korea	Retrospective	174	Pleural fluid	LPA, GeneXpert
Gupta et al.	2023	India	Prospective	302	Mixed EPTB samples	DST, LPA, GeneXpert
Ibrahim et al.	2020	Egypt	Cross-sectional	151	CSF	DST, GeneXpert
Perera et al.	2022	Sri Lanka	Prospective	128	Tissue biopsy	LPA, GeneXpert

Kumar et al.	2021	India	Retrospective	217	Lymph node aspirate	DST, GeneXpert
Ndlovu et al.	2019	South Africa	Cross-sectional	141	Pleural fluid	DST, LPA
Ortega et al.	2023	Peru	Prospective	194	Mixed EPTB samples	DST, LPA, GeneXpert
Rahman et al.	2024	Bangladesh	Prospective	226	Bone tissue	DST, GeneXpert

The pooled analysis demonstrated that GeneXpert MTB/RIF exhibited the highest diagnostic sensitivity among all evaluated modalities. The pooled sensitivity and specificity of GeneXpert MTB/RIF were 81.3% (95% CI: 76.4–85.2) and 97.8% (95% CI: 95.9–98.8), respectively. Line Probe Assay showed pooled sensitivity of 74.6% (95% CI: 68.2–80.1) and specificity of 98.5% (95% CI: 96.8–99.2). Conventional DST demonstrated comparatively lower sensitivity at 61.8% (95% CI: 55.4–67.8), although specificity remained highest at 99.1% (95% CI: 97.6–99.7).

The diagnostic odds ratio (DOR) and area under the summary receiver operating characteristic curve (AUC-SROC) were also highest for GeneXpert MTB/RIF, indicating superior overall diagnostic performance. Molecular assays demonstrated significantly lower negative likelihood ratios compared with conventional DST, suggesting better ability to exclude disease in suspected EPTB cases.

Table 2. Pooled Diagnostic Accuracy of Different Modalities

Diagnostic Method	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Diagnostic Odds Ratio	AUC-SROC
Conventional DST	61.8	99.1	68.7	0.39	89.4	0.82
Line Probe Assay	74.6	98.5	49.7	0.26	118.2	0.89
GeneXpert MTB/RIF	81.3	97.8	36.9	0.19	156.7	0.93

Subgroup analysis according to specimen type demonstrated substantial variability in diagnostic sensitivity among extrapulmonary samples. GeneXpert MTB/RIF showed highest sensitivity in lymph node aspirates (89.6%) and tissue biopsy specimens (90.2%). In cerebrospinal fluid samples, GeneXpert demonstrated sensitivity of 79.4%, significantly outperforming conventional DST and LPA. Pleural fluid and ascitic fluid specimens showed relatively lower sensitivity across all diagnostic methods due to low bacillary burden and reduced mycobacterial yield.

Conventional DST demonstrated particularly poor sensitivity in pleural and ascitic fluid specimens, whereas molecular assays maintained moderate diagnostic performance. LPA performed better in tissue-based specimens compared with serous fluids, likely because of higher bacillary concentration and improved DNA recovery.

Table 3. Diagnostic Accuracy According to Specimen Type

Specimen Type	Conventional DST Sensitivity (%)	LPA Sensitivity (%)	GeneXpert Sensitivity (%)
Lymph node aspirate	71.2	82.5	89.6
Cerebrospinal fluid	58.7	69.3	79.4
Pleural fluid	42.1	55.8	63.5
Tissue biopsy	73.4	81.6	90.2
Ascitic fluid	39.8	52.4	61.7
Bone and joint tissue	67.5	76.8	84.9

Analysis of rifampicin resistance detection showed that GeneXpert MTB/RIF demonstrated pooled sensitivity of 92.1% and specificity of 98.1%, closely comparable with Line Probe Assay, which demonstrated sensitivity of 90.4% and specificity of 98.7%. Conventional DST maintained highest specificity but required prolonged incubation and reporting times ranging from 3 to 8 weeks. In

contrast, GeneXpert MTB/RIF provided results within approximately two hours, while LPA required 1–2 days for resistance profiling.

Several studies reported excellent concordance between GeneXpert MTB/RIF and conventional phenotypic DST for rifampicin resistance detection. However, occasional discordant results were observed in paucibacillary specimens and samples with very low bacterial load.

Table 4. Performance for Rifampicin Resistance Detection

Diagnostic Method	Sensitivity (%)	Specificity (%)	Average Turnaround Time
Conventional DST	84.6	99.5	3–8 weeks
Line Probe Assay	90.4	98.7	1–2 days
GeneXpert MTB/RIF	92.1	98.1	~2 hours

Moderate-to-high heterogeneity was observed among included studies, with pooled I^2 values ranging from 48% to 72%. Heterogeneity was mainly attributed to differences in specimen processing techniques, geographical distribution, HIV prevalence, bacillary load, and reference standards used across studies. Studies using composite reference standards generally reported higher pooled sensitivity than studies using culture alone as the gold standard.

Quality assessment using QUADAS-2 demonstrated overall moderate-to-high methodological quality. Most studies showed low risk of bias in index test interpretation and reference standard domains, although some retrospective studies demonstrated unclear risk related to patient selection and incomplete outcome reporting.

Table 5. Quality Assessment of Included Studies Using QUADAS-2

Domain	Low Risk (%)	Unclear Risk (%)	High Risk (%)
Patient Selection	73.8	19.0	7.2
Index Test	88.1	9.5	2.4
Reference Standard	83.3	11.9	4.8
Flow and Timing	78.6	16.7	4.7

Publication bias assessment using funnel plot analysis did not demonstrate significant asymmetry. Egger's regression test also revealed no statistically significant small-study effect ($p > 0.05$), indicating acceptable robustness of pooled estimates.

Overall, GeneXpert MTB/RIF emerged as the most clinically useful diagnostic modality for extrapulmonary tuberculosis because of its superior sensitivity, excellent specificity, rapid turnaround time, and ability to simultaneously detect rifampicin resistance. While conventional DST remains essential for comprehensive phenotypic drug susceptibility profiling, molecular assays substantially improved early diagnosis and treatment initiation in extrapulmonary tuberculosis cases.

DISCUSSION

The present systematic review and meta-analysis comprehensively compared the diagnostic performance of conventional drug susceptibility testing (DST), Line Probe Assay (LPA), and GeneXpert MTB/RIF in extrapulmonary tuberculosis (EPTB). The findings demonstrated that GeneXpert MTB/RIF exhibited the highest pooled sensitivity and overall diagnostic accuracy among the evaluated modalities, while conventional DST maintained the highest specificity but comparatively lower sensitivity and significantly prolonged turnaround time. These findings highlight the growing importance of rapid molecular diagnostics in improving early detection and management of extrapulmonary tuberculosis.

Diagnosis of EPTB remains challenging because of the paucibacillary nature of extrapulmonary specimens and the heterogeneous clinical manifestations associated with different anatomical sites [16]. Conventional microbiological methods such as smear microscopy and culture-based DST often demonstrate limited sensitivity in extrapulmonary samples because of low bacterial burden and difficulties in specimen collection [17]. In the present meta-analysis, conventional DST demonstrated pooled sensitivity of only 61.8%, which was substantially lower than both GeneXpert MTB/RIF and LPA. Similar findings have been reported in previous studies where culture positivity rates in pleural and cerebrospinal fluid specimens remained relatively low despite confirmed clinical disease [18].

GeneXpert MTB/RIF demonstrated superior pooled sensitivity of 81.3% with excellent specificity of 97.8%, making it the most effective overall diagnostic modality evaluated in this analysis. The improved performance of GeneXpert may be attributed to automated real-time polymerase chain reaction technology capable of detecting minute quantities of Mycobacterium tuberculosis DNA [19]. Several previous meta-analyses have similarly demonstrated high diagnostic accuracy of

GeneXpert in EPTB, particularly in lymph node tuberculosis and tuberculous meningitis [20,21]. The rapid turnaround time of approximately two hours provides significant clinical advantage by facilitating early initiation of anti-tubercular therapy and reducing diagnostic delay.

The present study also demonstrated that diagnostic accuracy varied substantially according to specimen type. GeneXpert MTB/RIF showed highest sensitivity in tissue biopsy and lymph node aspirate specimens, while lower sensitivity was observed in pleural and ascitic fluid samples. This variation is likely related to differences in bacillary concentration among extrapulmonary specimens [22]. Fluid-based specimens typically contain fewer bacilli compared with tissue specimens, thereby reducing sensitivity of both molecular and culture-based assays [23]. Similar observations have been reported by Denkinger et al., who found significantly higher sensitivity of GeneXpert in lymph node and tissue specimens compared with serous fluids [24].

Line Probe Assay demonstrated pooled sensitivity of 74.6% and specificity of 98.5% in the present analysis. Although slightly less sensitive than GeneXpert MTB/RIF, LPA remains an important diagnostic tool for rapid detection of drug-resistant tuberculosis. LPA provides the additional advantage of simultaneous detection of rifampicin and isoniazid resistance-associated mutations, which is particularly valuable in multidrug-resistant tuberculosis (MDR-TB) endemic settings [25]. However, the performance of LPA may be limited in extrapulmonary specimens with low bacillary load because adequate DNA concentration is necessary for optimal amplification and hybridization [26].

An important finding of the present study was the excellent performance of molecular assays for detection of rifampicin resistance. GeneXpert MTB/RIF demonstrated pooled sensitivity of 92.1% for rifampicin resistance detection, closely comparable with LPA. Early identification of rifampicin resistance is clinically significant because rifampicin resistance is considered a reliable surrogate marker for multidrug-resistant tuberculosis [27]. Rapid resistance detection allows timely initiation of appropriate second-line anti-tubercular therapy and may reduce transmission of resistant strains within the community [28].

Although conventional DST demonstrated lower sensitivity and prolonged turnaround time, it continues to play a critical role in comprehensive phenotypic drug susceptibility assessment. Molecular assays primarily detect known genetic mutations associated with resistance; however, rare or novel mutations may occasionally remain undetected [29]. Conventional culture-based DST therefore remains essential for confirmation of molecular resistance profiles and evaluation of susceptibility to second-line anti-tubercular agents [30]. Integration of molecular diagnostics with conventional phenotypic methods may therefore provide the most effective diagnostic strategy for EPTB management.

Moderate heterogeneity observed across included studies may be explained by variations in specimen processing methods, laboratory protocols, patient populations, HIV prevalence, and reference standards used among studies [31]. Studies utilizing composite reference standards generally demonstrated higher pooled sensitivity than those using culture alone because culture methods themselves possess imperfect sensitivity in paucibacillary EPTB [32]. Furthermore, differences in sample storage, nucleic acid extraction techniques, and operator expertise may also have contributed to inter-study variability.

The findings of this meta-analysis have important clinical and public health implications. Early and accurate diagnosis of extrapulmonary tuberculosis is critical for reducing morbidity, mortality, and long-term complications associated with delayed treatment [33]. Molecular diagnostic tools such as GeneXpert MTB/RIF can substantially improve diagnostic efficiency in resource-limited settings where access to advanced mycobacterial culture laboratories remains limited [34]. The WHO currently recommends GeneXpert MTB/RIF as an initial diagnostic test for several forms of extrapulmonary tuberculosis, particularly tuberculous meningitis and lymph node TB [35]. The present study further supports these recommendations by demonstrating superior overall diagnostic performance of GeneXpert compared with conventional DST and LPA.

The present study has several limitations. Significant heterogeneity existed among included studies with respect to study design, specimen type, and reference standards. Some studies included clinically diagnosed EPTB cases without microbiological confirmation, which may have influenced pooled diagnostic estimates [36]. Additionally, limited data were available regarding pediatric populations, HIV coinfection status, and performance of newer molecular assays such as Xpert Ultra. Publication bias, although statistically nonsignificant, cannot be completely excluded.

Despite these limitations, the present meta-analysis provides comprehensive comparative evidence regarding the diagnostic performance of conventional DST, LPA, and GeneXpert MTB/RIF in extrapulmonary tuberculosis. The findings strongly support the increasing role of rapid molecular diagnostics in improving early diagnosis and management of EPTB, while emphasizing the continued importance of conventional DST for comprehensive resistance profiling and treatment guidance.

CONCLUSION

GeneXpert MTB/RIF demonstrated superior overall diagnostic performance compared with Line Probe Assay and conventional DST in extrapulmonary tuberculosis cases. Its rapid turnaround time, high specificity, and improved sensitivity make it an effective frontline diagnostic tool for EPTB. Although conventional DST remains indispensable for comprehensive drug-resistance characterization, molecular assays substantially improve early diagnosis and treatment initiation. Integration of GeneXpert MTB/RIF with conventional microbiological methods may provide the most effective diagnostic strategy for extrapulmonary tuberculosis.

Ethical Approval

Not applicable, as this study was based on previously published literature.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No external funding was received for this study.

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How to cite this article: Subhasish Chanda, Sanjay Kumar Yadav, Yogesh Tamang, DIAGNOSTIC PERFORMANCE OF MOLECULAR AND CONVENTIONAL METHODS FOR EXTRAPULMONARY TUBERCULOSIS DETECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS, Asian J. Med. Res. Health Sci., 2026; 4 (2):-142-149.
Source of Support: Nil, Conflicts of Interest: None declared.